



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 30

A. R. Katritzky

Advances in
**Heterocyclic
Chemistry**

Volume 30

Editorial Advisory Board

R. A. Abramovitch

A. Albert

A. T. Balaban

A. J. Boulton

S. Gronowitz

T. Kametani

C. W. Rees

Yu. N. Sheinker

M. Tišler

Advances in

HETEROCYCLIC CHEMISTRY

Edited by

A. R. KATRITZKY

*Department of Chemistry
University of Florida
Gainesville, Florida*



ACADEMIC PRESS, INC.
Harcourt Brace Jovanovich, Publishers
San Diego New York Berkeley Boston
London Sydney Tokyo Toronto

Volume 30

COPYRIGHT © 1982, BY ACADEMIC PRESS, INC.

ALL RIGHTS RESERVED.

NO PART OF THIS PUBLICATION MAY BE REPRODUCED OR
TRANSMITTED IN ANY FORM OR BY ANY MEANS, ELECTRONIC
OR MECHANICAL, INCLUDING PHOTOCOPY, RECORDING, OR ANY
INFORMATION STORAGE AND RETRIEVAL SYSTEM, WITHOUT
PERMISSION IN WRITING FROM THE PUBLISHER.

ACADEMIC PRESS, INC.

1250 Sixth Avenue, San Diego, California 92101

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 62-13037

ISBN 0-12-020630-7

PRINTED IN THE UNITED STATES OF AMERICA

88 89 90 91 92

10 9 8 7 6 5 4 3 2

Contents

| | |
|------------------------|-----|
| CONTRIBUTORS | vii |
| PREFACE | ix |

Azodicarbonyl Compounds in Heterocyclic Synthesis

CHRISTOPHER J. MOODY

| | |
|--|----|
| I. Introduction | 1 |
| II. Preparation of Azodicarbonyl Derivatives | 2 |
| III. General Reactivity of Azodicarbonyl Compounds | 6 |
| IV. Use of Azodicarbonyl Compounds in Heterocyclic Synthesis | 10 |
| V. Other Reactions of Azodicarbonyl Compounds | 41 |
| VI. Conclusion | 44 |

Sulfur Transfer Reagents in Heterocyclic Synthesis

MICHAEL DAVIS

| | |
|---|----|
| I. Introduction | 48 |
| II. Hydrogen Sulfide, Sodium Sulfide, and Other Inorganic Salts | 49 |
| III. Elemental Sulfur | 53 |
| IV. Sulfur Halides and Related Compounds of Divalent Sulfur | 55 |
| V. Tetravalent Sulfur Compounds | 60 |
| VI. Hexavalent Sulfur Compounds | 71 |
| VII. Thiocarbonyl Compounds | 73 |
| VIII. Phosphorus Sulfides | 75 |

Heteroadamantane

TADASHI SASAKI

| | |
|--|-----|
| I. Introduction | 80 |
| II. Heteroadamantanes Involving Nitrogen | 81 |
| III. Heteroadamantanes Involving Oxygen | 98 |
| IV. Heteroadamantanes Involving Sulfur | 111 |
| V. Heteroadamantanes Involving Two or More Heteroatoms | 118 |

Selenophenes

ANNA-BRITTA HÖRNFELDT

| | |
|--|-----|
| I. Introduction | 127 |
| II. Theoretical Treatment | 128 |
| III. Dipole Moments | 129 |
| IV. Determination of Geometries and Conformations | 129 |
| V. Spectroscopic Studies | 131 |
| VI. Preparation of Selenophenes | 136 |
| VII. Electrophilic and Nucleophilic Substitution Reactions | 141 |
| VIII. Reactions via Organometallic Intermediates | 145 |
| IX. Carbonyl-Substituted Derivatives of Selenophene | 149 |
| X. Hydroxyselenophenes and Their Sulfur and Selenium Analogs | 155 |
| XI. Selenophenes with Nitrogen-Containing Substituents | 158 |
| XII. Selenophenes of Potential Technical Utility | 164 |
| XIII. Miscellaneous | 166 |

Recent Advances in Furan Chemistry. Part I

FRANCIS M. DEAN

| | |
|--|-----|
| I. Introduction | 168 |
| II. Syntheses of the Furan Ring | 169 |
| III. Ionic Attack | 191 |
| IV. Lithium, Boron, and Other Elements | 207 |
| V. Radical Chemistry | 216 |
| VI. Oxidation and Reduction | 226 |

Photochemistry of Nitrogen-Containing Heterocycles

S. T. REID

| | |
|---|-----|
| I. Introduction | 239 |
| II. Bond Cleavage and Rearrangement | 240 |
| III. Photoaddition | 278 |
| IV. Photocyclization | 292 |
| V. Photoelimination | 305 |

Use of Transition Organometallic Compounds in Heterocyclic Synthesis

J. L. DAVIDSON AND P. N. PRESTON

| | |
|---|-----|
| I. Introduction | 321 |
| II. Three-Membered Ring Compounds | 324 |
| III. Four-Membered Ring Compounds | 326 |
| IV. Five-Membered Ring Compounds | 330 |
| V. Six-Membered Ring Compounds | 376 |
| VI. Seven-Membered Ring Compounds | 396 |
| VII. Macrocycles | 402 |
| CUMULATIVE INDEX OF TITLES | 403 |

Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

J. L. DAVIDSON, *Department of Chemistry, Heriot-Watt University, Riccarton, Currie, Edinburgh EH14 4AS, Scotland* (319)

MICHAEL DAVIS, *Department of Organic Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia* (47)

FRANCIS M. DEAN, *Department of Organic Chemistry, University of Liverpool, Liverpool L69 3BX, England* (167)

ANNA-BRITTA HÖRNFELDT, *Department of Organic Chemistry, 1 Chemical Center, University of Lund, Lund, Sweden* (127)

CHRISTOPHER J. MOODY, *Department of Chemistry, Imperial College of Science and Technology, London SW7 2AY, England* (1)

P. N. PRESTON, *Department of Chemistry, Heriot-Watt University, Riccarton, Currie, Edinburgh EH14 4AS, Scotland* (319)

S. T. REID, *University Chemical Laboratory, University of Kent at Canterbury, Canterbury, Kent CT2 NH7, England* (239)

TADASHI SASAKI, *Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Nagoya, Japan* (79)

This Page Intentionally Left Blank

Preface

Volume 30 contains seven chapters. That dealing with "Furans" by F. M. Dean updates the review entitled "The Development of the Chemistry of Furans 1952–1963" by F. Bosshard and C. H. Eugster which was published in Volume 7.

Dr. S. T. Reid has contributed the first of two sections on photochemistry of heterocycles, the present one dealing with that of *N*-heterocycles. This updates part of his own earlier review "The Photochemistry of Heterocycles" published in 1970 in Volume 11. A further contribution, which will extend the updating to *O*- and *S*-heterocycles, should be published shortly. Dr. A. B. Hornfeldt's review, entitled "Selenophenes," also deals with a subject that was previously reviewed in Volume 12 of this series by N. N. Magdesieva.

The remaining four chapters of the present volume involve topics new to the series. Two of them deal with specific groups of compounds (C. J. Moody on "Azodicarbonyl Compounds" and T. Sasaki on "Heteroadamantanes") and two others deal with the "Use of Transition Organometallic Compounds in Heterocyclic Synthesis" (J. L. Davidson and P. N. Preston) and "Sulfur Transfer Reagents" (M. Davis).

A. R. KATRITZKY

This Page Intentionally Left Blank

Azodicarbonyl Compounds in Heterocyclic Synthesis

CHRISTOPHER J. MOODY

*Department of Chemistry, Imperial College of Science and Technology,
London, England*

| | |
|--|----|
| I. Introduction | 1 |
| II. Preparation of Azodicarbonyl Compounds | 2 |
| A. Acyclic Derivatives | 2 |
| B. Cyclic Derivatives | 3 |
| III. General Reactivity of Azodicarbonyl Compounds | 6 |
| A. Reaction with Dienes | 6 |
| B. Reaction with Monoenes | 8 |
| C. Reaction with 1,3-Dipoles | 10 |
| D. Reaction with Nucleophiles | 10 |
| IV. Use of Azodicarbonyl Compounds in Heterocyclic Synthesis | 10 |
| A. Preparation of Three-Membered Rings | 10 |
| B. Preparation of Four-Membered Rings | 13 |
| C. Preparation of Five-Membered Rings. | 19 |
| 1. Reaction with 1,3-Dipoles | 19 |
| 2. Reaction with Carbenes | 24 |
| 3. Reaction with Nucleophiles | 25 |
| 4. Miscellaneous | 29 |
| D. Preparation of Six-Membered Rings | 30 |
| 1. Reaction with Dienes | 30 |
| 2. Preparation of Cyclic Azoalkanes | 36 |
| 3. Reaction with Monoenes | 38 |
| 4. By Further Transformation of Initial Adducts | 39 |
| E. Preparation of Larger Rings | 40 |
| V. Other Reactions of Azodicarbonyl Compounds. | 41 |
| A. Protection of Dienes | 41 |
| B. Interception of Reactive Dienes. | 43 |
| C. Other Reactions | 44 |
| VI. Conclusion | 44 |

I. Introduction

Azodicarbonyl compounds, which contain a carbonyl function on both sides of the azo bond, in contrast to aliphatic and aromatic azo compounds, possess a highly reactive $\text{N}=\text{N}$ group. In recent years they have found wide

use as reactive dienophiles, enophiles, and electrophiles. Many of their reactions lead to heterocyclic products and are preparatively useful, and it is on this aspect that this review will concentrate. Reactions in which one, or both, of the nitrogen atoms of the azo group are retained in the final heterocyclic product are considered, and are classified according to the size of the new ring formed. Other reactions of azodicarbonyl (ADC) compounds, which do not give heterocyclic products, are discussed briefly in Section V.

The chemistry of α -carbonyl azo compounds was the subject of a comprehensive review in 1966.¹ More recently, certain aspects of the chemistry of ADC compounds have been reviewed.²⁻⁴ The present chapter surveys the literature from 1966 to mid-1980.

II. Preparation of Azodicarbonyl Compounds

A. ACYCLIC DERIVATIVES

Acyclic ADC compounds, which are more correctly named as derivatives of diazene, are generally prepared from hydrazine derivatives. For example, diethyl azodicarboxylate (*Chemical Abstracts* name: diethyl diazene-1,2-dicarboxylate)⁵ is prepared from hydrazine by treatment with ethyl chloroformate followed by oxidation with chlorine in benzene-water.⁶ Other oxidants which have been used include *N*-bromosuccinimide,⁷ nitric acid,⁸ inorganic nitrates,⁹ potassium dichromate,¹⁰ silver carbonate on celite,¹¹ and phenyl iodosotrifluoroacetate.¹² The hydrazine derivative may also be

¹ E. Fahr and H. Lind, *Angew. Chem., Int. Ed. Engl.* **5**, 372 (1966).

² K. MacKenzie, in "The Chemistry of the Hydrazo, Azo and Azoxy Groups" (S. Patai, ed.), Chapter 11. Wiley, New York, 1975.

³ G. Bianchi, C. de Micheli, and R. Gandolfi, in "The Chemistry of the Double Bonded Functional Groups" (S. Patai, ed.), Part 1, Chapter 6. Wiley, New York, 1977; A. P. Marchand, *ibid.*, Chapter 7.

⁴ M. Quinteiro, C. Seoane, and J. L. Soto, *Heterocycles* **9**, 1771 (1978).

⁵ Diethyl azodicarboxylate is usually abbreviated to DEAD. However, the same abbreviation is used for diethyl acetylenedicarboxylate. To avoid confusion, it is proposed that DEAZD should be used to abbreviate the azo ester. Similarly, DMAZD will be used for the dimethyl ester. Recently, the abbreviation DAZD has also been suggested: B. M. Jacobson, D. Gerhard, C. Jackson, and J. Smallwood, *J. Org. Chem.* **45**, 3344 (1980).

⁶ N. Rabjohn, *Org. Synth.* **28**, 58 (1948).

⁷ L. A. Carpino, P. H. Terry, and P. J. Crowley, *J. Org. Chem.* **26**, 4336 (1961); L. A. Carpino and P. J. Crowley, *Org. Synth.* **44**, 18 (1964).

⁸ H. Böshagen and J. Ullrich, *Chem. Ber.* **92**, 1478 (1959).

⁹ Wallace and Tiernan, Inc., British Patent 873,597 (1960).

¹⁰ A. T. d'Arcangelo, *Rev. Fac. Cienc. Quim., Univ. Nac. La Plata* **18**, 81 (1943) [*CA* **41**, 948 (1947)].

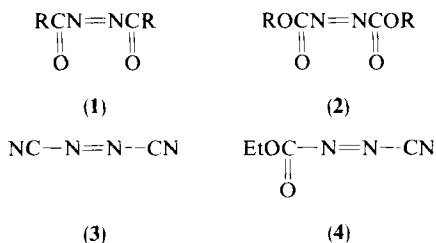
¹¹ M. Fetizon, M. Golfier, R. Milcent, and L. Papadakis, *Tetrahedron* **31**, 165 (1975).

¹² S. Spyroudis and A. Varvoglis, *Synthesis*, 445 (1975).

oxidized by reaction with mercury(II) chloride, followed by treatment of the metal derivative with iodine or bromine.¹³ Azodicarboxamides are readily prepared from diethyl azodicarboxylate (DEAZD⁵) and the corresponding amines.¹⁴

The acyclic ADC compounds **1** and **2** are usually isolable, and reasonably stable, although the trifluoromethyl derivative (**1**, R = CF₃) is reported to be unstable.¹⁵ In general, the diesters **2** have found greatest use in synthesis, with DEAZD (**2**, R = Et) being the most commonly used; it is available commercially.

The related compounds 1,2-dicyanodiazene (**3**),¹⁶ and ethyl 1-cyano-diazene-2-carboxylate (**4**)¹⁷ have also been reported and show similar reactivity to ADC compounds.



B. CYCLIC DERIVATIVES

Cyclic ADC compounds are similarly prepared by oxidation of the corresponding cyclic hydrazine derivatives. The most commonly encountered compounds are the 3*H*-1,2,4-triazole-3,5(4*H*)-diones (**5**), and in particular the 4-phenyl derivative (**5**, R = Ph), usually abbreviated as PTAD. Similarly, the abbreviation MTAD is used for the 4-methyl derivative. First prepared by Thiele,¹⁸ PTAD remained unused in organic synthesis until Cookson reported its powerful dienophilic properties some 70 years later.¹⁹ PTAD is an isolable, red, crystalline compound, prepared by *t*-butyl hypochlorite oxidation of 4-phenylurazole.²⁰ Other oxidants which have been successfully

¹³ D. Y. Curtin and T. C. Miller, *J. Org. Chem.* **25**, 885 (1960).

¹⁴ O. Diels and P. Fritzsche, *Ber. Dtsch. Chem. Ges.* **44**, 3018 (1911); E. E. Smissman and A. Makriyannis, *J. Org. Chem.* **38**, 1652 (1973).

¹⁵ J. A. Young, W. S. Durrell, and R. D. Dresdner, *J. Am. Chem. Soc.* **84**, 2105 (1962).

¹⁶ F. D. Marsh and M. E. Hermes, *J. Am. Chem. Soc.* **87**, 1819 (1965).

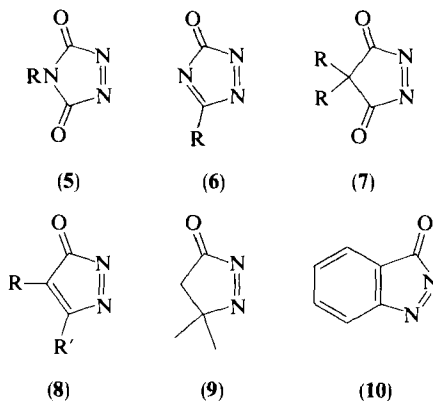
¹⁷ J. Harley-Mason and J. C. W. Tims, *Proc. Chem. Soc., London*, 345 (1963).

¹⁸ J. Thiele and O. Stange, *Justus Liebigs Ann. Chem.* **283**, 1 (1894).

¹⁹ R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Lett.*, 615 (1962); R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc. C*, 1905 (1967).

²⁰ R. C. Cookson, S. S. Gupte, I. D. R. Stevens, and C. T. Watts, *Org. Synth.* **51**, 121 (1971).

used include lead dioxide,¹⁸ lead tetraacetate,²¹ dinitrogen tetroxide,²² tosyl isocyanate in dimethyl sulfoxide,²³ *N*-bromosuccinimide,²⁴ and benzene-seleninic anhydride.²⁵ A wide range of 4-substituted derivatives has now been prepared, although references to the 4-phenyl derivative outnumber all the others combined. The parent compound (**5**, R = H) has not been isolated, but can be generated and reacted *in situ*.^{26,27} The related monocarbonyl compounds (**6**) have been generated, although little used.²⁸



The 3*H*-pyrazole-3,5(4*H*)-diones (**7**), prepared by lead tetraacetate,^{29,30} or *tert*-butyl hypochlorite^{31,32} oxidation of malonic acid cyclic hydrazides, are generally less stable than the triazoles **5**, and are not isolable. The monocarbonyl derivatives (**8**–**10**) have been reported.^{33–36} The unstable 1,3,4-thiadiazole-2,5-dione (**11**) has been generated and reacted *in situ*.^{37,38}

²¹ B. T. Gillis and J. D. Hagarty, *J. Org. Chem.* **32**, 330 (1967).

²² J. C. Stickler and W. H. Pirkle, *J. Org. Chem.* **31**, 3444 (1966).

²³ J. A. Moore, R. Muth, and R. Sorace, *J. Org. Chem.* **39**, 3799 (1974).

²⁴ H. Wamhoff and K. Wald, *Org. Prep. Proced. Int.* **7**, 251 (1975).

²⁵ D. H. R. Barton, D. J. Lester, and S. V. Ley, *J. C. S. Chem. Commun.*, 276 (1978).

²⁶ M. G. Amezuza, M. Lora-Tamayo, and J. L. Soto, *Tetrahedron Lett.*, 2407 (1970).

²⁷ J. E. Herweh and R. M. Fantazier, *Tetrahedron Lett.*, 2101 (1973).

²⁸ B. T. Gillis and J. G. Dain, *J. Org. Chem.* **36**, 518 (1971).

²⁹ B. T. Gillis and R. A. Izydore, *J. Org. Chem.* **34**, 3181 (1969).

³⁰ H. Stetter and P. Woermle, *Justus Liebigs Ann. Chem.* **724**, 150 (1969).

³¹ A. B. Evnin, A. Y. Lam, J. J. Maher, and J. J. Blyskal, *Tetrahedron Lett.*, 4497 (1969).

³² M. G. Amezuza, M. Lora-Tamayo, M. Pardo, and J. L. Soto, *An. Quim.* **71**, 396 (1975).

³³ L. A. Carpino, P. H. Terry, and S. D. Thatte, *J. Org. Chem.* **31**, 2867 (1966); C. W. Rees and M. Yelland, *J. C. S. Perkin I*, 221 (1973).

³⁴ B. T. Gillis and R. Weinkam, *J. Org. Chem.* **32**, 3321 (1967).

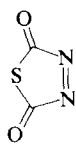
³⁵ W. Nagata and S. Kamata, *J. Chem. Soc. C*, 540 (1970).

³⁶ E. F. Ullman and E. A. Barkus, *Chem. Ind. (London)*, 93 (1962); D. L. Forster, T. L. Gilchrist, C. W. Rees, and E. Stanton, *J. C. S. Chem. Commun.*, 695 (1971).

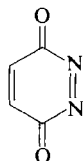
³⁷ E. J. Corey and B. B. Snider, *J. Org. Chem.* **38**, 3632 (1973).

³⁸ S. W. Mojé and P. Beak, *J. Org. Chem.* **39**, 2951 (1974).

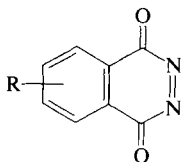
Six-membered ring ADC compounds can be generated by oxidation of the corresponding cyclic hydrazides. Pyridazine-3,6-dione (**12**) and phthalazine-1,4-dione (**13**, R = H), often called diazaquinones,⁴ are stable in solution only at low temperature, but can be generated, and intercepted at higher temperatures.^{39–43} Fusion of an extra benzene ring increases stability,⁴⁴ and the tetracyclic compound **14** is relatively stable.⁴⁵ Substituted phthalazine-1,4-diones have been widely studied because of their involvement in



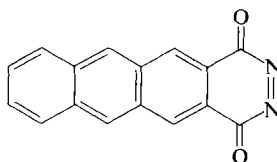
(11)



(12)

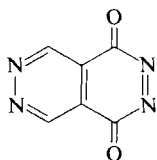


(13)

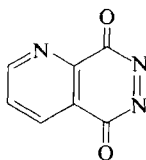


(14)

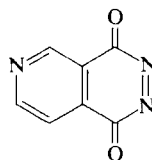
certain chemiluminescent reactions (e.g., Refs. 45 and 46). Derivatives in which the diazaquinone is fused to a heterocyclic ring have also been generated: for example, compounds of type **15**,⁴⁷ **16–20**,⁴⁸ and **21–23**⁴⁹ are known.



(15)



(16)



(17)

³⁹ R. A. Clement, *J. Org. Chem.* **25**, 1724 (1960).

⁴⁰ R. A. Clement, *J. Org. Chem.* **27**, 1115 (1962).

⁴¹ T. J. Kealy, *J. Am. Chem. Soc.* **84**, 966 (1962).

⁴² M. F. Brana, M. Lora-Tamayo, P. Navarro, and J. L. Soto, *Tetrahedron Lett.*, 1523 (1969).

⁴³ A. Landa, C. Seoane, and J. L. Soto, *An. Quim.* **70**, 962 (1974).

⁴⁴ E. H. White, E. G. Nash, D. R. Roberts, and O. C. Zafiriou, *J. Am. Chem. Soc.* **90**, 5932 (1968).

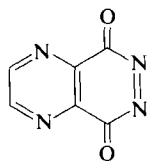
⁴⁵ K. D. Gundermann, H. Fiege, and G. Klockenbring, *Justus Liebigs Ann. Chem.* **738**, 140 (1970); K. D. Gundermann, *Angew. Chem., Int. Ed. Engl.* **7**, 480 (1968).

⁴⁶ Y. Omote, T. Miyake, and N. Sugiyama, *Bull. Chem. Soc. Jpn.* **40**, 2446 (1967); E. H. White, D. F. Roswell, and O. C. Zafiriou, *J. Org. Chem.* **34**, 2462 (1969).

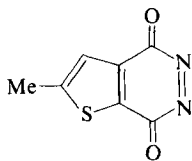
⁴⁷ G. Adembris, F. DeSio, R. Nesi, and M. Scotton, *J. Chem. Soc. C*, 2857 (1968).

⁴⁸ M. G. Amezuza, M. Lora-Tamayo, J. L. Soto, and E. D. Toro, *An. Quim.* **66**, 561 (1970).

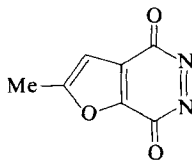
⁴⁹ B. T. Gillis and J. C. Valentour, *J. Heterocycl. Chem.* **8**, 13 (1971).



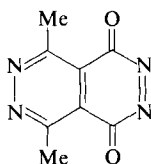
(18)



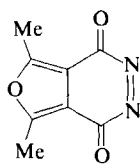
(19)



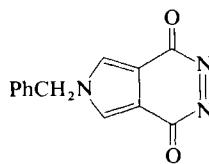
(20)



(21)



(22)



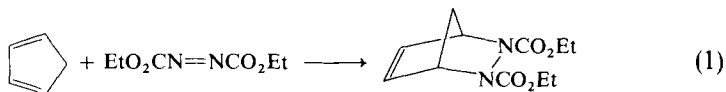
(23)

III. General Reactivity of Azodicarbonyl Compounds

The most important aspect of ADC compounds, as far as heterocyclic synthesis is concerned, is the great reactivity of the $N=N$ bond in cycloaddition reactions with dienes, monoenes and 1,3-dipoles, and as an electrophile. Other aspects of ADC reactivity are discussed briefly in Section V.

A. REACTION WITH DIENES

The first use of DEAZD as a dienophile was reported by Diels in 1925.⁵⁰ The reaction with cyclopentadiene was highly exothermic, and gave a high yield of the Diels–Alder adduct (Eq. 1). The reaction of DEAZD with cyclohexadiene depends on the conditions (see Section III,B and also Ref. 1).



(1)

Kinetic studies on the reaction of azodicarboxylates with cyclopentadiene have shown that the dimethyl ester, DMAZD, reacts 5–6 times more rapidly than DEAZD.⁵¹ The bulky *tert*-butyl ester (**2**, $R = t\text{-Bu}$) reacted only slowly with cyclopentadiene.⁷ The reaction proceeds faster in polar than in nonpolar

⁵⁰ O. Diels, J. H. Blom, and W. Koll, *Justus Liebigs Ann. Chem.* **443**, 242 (1925).

⁵¹ A. Rodgman and G. F. Wright, *J. Org. Chem.* **18**, 465 (1953).

solvents, and is also accelerated by the addition of acid.^{51,52} Azodiaroyls (1, R = Ar) also react readily with dienes in a Diels–Alder fashion, the reaction being accelerated by the presence of electron-withdrawing groups on the aromatic ring.⁵³

Like azobenzene, DEAZD is believed to exist in the trans form, but can be partially converted into the cis form by UV radiation. Thus, irradiation of DEAZD at 300 nm gave a mixture which contained approximately 30% cis form. The cis form is much more reactive than the trans, the relative rates of reaction with cyclopentadiene being approximately 100:1.⁵⁴

In general, the N=N dienophiles are more reactive than the corresponding C=C compounds, because of their low energy LUMOs. As with carbon dienophiles, incorporation of the ADC system into a ring lowers the LUMO energy still further, and therefore the cyclic ADC compounds, in which the N=N bond is necessarily cis, are highly reactive dienophiles. As a class, the 4-substituted 1,2,4-triazole-3,5-diones (5) are probably the most powerful dienophiles known.^{19,55,56} For example, the rate constants for the reaction of PTAD with various “unreactive” dienes exceed those for the corresponding reactions of tetracyanoethene (TCNE) by as much as 10⁴ in some cases.⁵⁷ This markedly superior reactivity of PTAD extends to other reactions, although TCNE is thought to be more reactive than PTAD as an electrophile.⁵⁸ Substituent and solvent effects on the Diels–Alder reaction have been studied. The 4-(4-nitrophenyl) derivative (5, R = 4-NO₂C₆H₄) is the most reactive, and the reaction proceeds particularly well in benzene or dioxane,⁵⁶ although chlorinated solvents are reported to be better.⁵⁹ Secondary orbital interactions between the N=N bond and the substrate are thought to be important in some cases; this explains the observed stereochemical differences in the reactions of PTAD and the corresponding C=C dienophile, *N*-phenylmaleimide, with propellanes (e.g., see Ref. 60).

⁵² L. E. Gast, E. W. Bell, and H. M. Teeter, *J. Am. Oil Chem. Soc.* **33**, 278 (1956).

⁵³ Y. S. Shabarov, N. I. Vasil'ev, I. S. Levina, and R. Y. Levina, *J. Gen. Chem. USSR (Engl. Transl.)* **32**, 2764 (1962); N. I. Vasil'ev, I. S. Levina, Y. S. Shabarov, and R. Y. Levina, *ibid.* **33**, 723 (1963).

⁵⁴ G. O. Schenck, H. R. Kopp, B. Kim, and E. K. von Gustorf, *Z. Naturforsch., B; Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **20B**, 637 (1965); R. Askani, *Chem. Ber.* **98**, 2551 (1965).

⁵⁵ J. Sauer, *Angew. Chem., Int. Ed. Engl.* **6**, 16 (1967).

⁵⁶ M. E. Burrage, R. C. Cookson, S. S. Gupte, and I. D. R. Stevens, *J. C. S. Perkin II*, 1325 (1975).

⁵⁷ J. Sauer and B. Schröder, *Chem. Ber.* **100**, 678 (1967).

⁵⁸ H. Hogeveen and L. Zwart, *J. Org. Chem.* **44**, 1365 (1979).

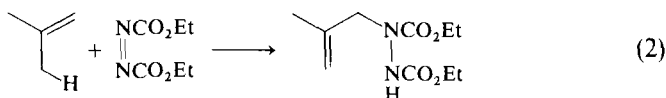
⁵⁹ A. I. Konovalov, I. P. Breus, I. A. Sharagin, and V. D. Kiselev, *J. Org. Chem. USSR (Engl. Transl.)* **15**, 315 (1979).

⁶⁰ M. Kaftory, M. Peled, and D. Ginsburg, *Helv. Chim. Acta* **62**, 1326 (1979).

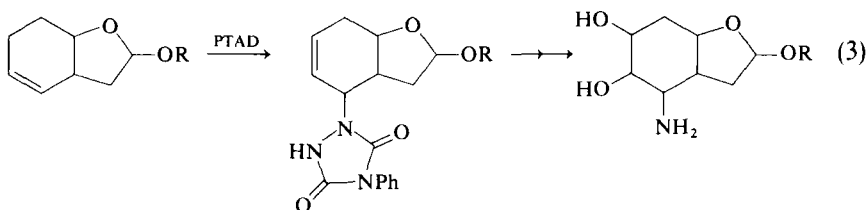
It is the combination of exceptional reactivity and reasonable stability, either as a solid or in solution, that makes PTAD such an ideal dienophile. However, PTAD is decomposed to N_2 , CO and phenyl isocyanate by the action of UV light.⁶¹ The cyclic ADC compounds (**6–23**) all undergo the Diels–Alder reaction, although with the exception of phthalazine-1,4-dione (**13**, $R = H$), they have been used only occasionally. 1,3,4-Thiadiazole-2,5-dione (**11**) is of comparable reactivity to PTAD,³⁸ but like the other cyclic compounds (**6–23**) has the slight disadvantage in that it has to be generated *in situ*.

B. REACTION WITH MONOENES

The $N=N$ bond in ADC compounds also reacts rapidly in the ene reaction (for a review, see Ref. 62). For example, DEAZD reacts with 2-methylpropene to give the ene product (Eq. 2). In certain cases the ene



reaction predominates even when the possibility for 1,4 (Diels–Alder) addition exists. Cyclohexadiene and DEAZD can give the ene product, diethyl 1-(cyclohexa-1,4-dien-3-yl)hydrazine-1,2-dicarboxylate, in up to 80% yield, with only traces of the normal Diels–Alder product formed.⁶³ PTAD also enters readily into the ene reaction,⁶⁴ and the reaction has been used as a method of introducing an amino group (Eq. 3),⁶⁵ and as a non-catalytic method of shifting a double bond (Eq. 4).⁶⁶



⁶¹ H. Wamhoff and K. Wald, *Chem. Ber.* **110**, 1699 (1977).

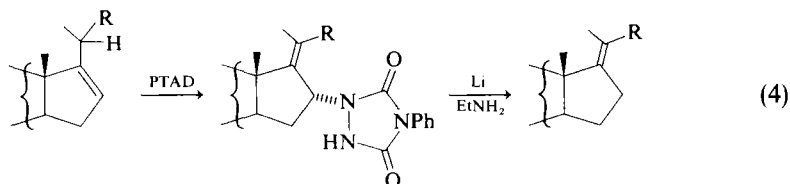
⁶² H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **8**, 556 (1969).

⁶³ B. Franzus and J. H. Surridge, *J. Org. Chem.* **27**, 1951 (1962); B. Franzus, *ibid.* **28**, 2954 (1963); B. T. Gillis and P. E. Beck, *ibid.* **27**, 1947 (1962).

⁶⁴ W. H. Pirkle and J. C. Stickler, *J. C. S. Chem. Commun.*, 760 (1967); S. Sarel, A. Felzenstein, and J. Yovell, *ibid.*, 859 (1973).

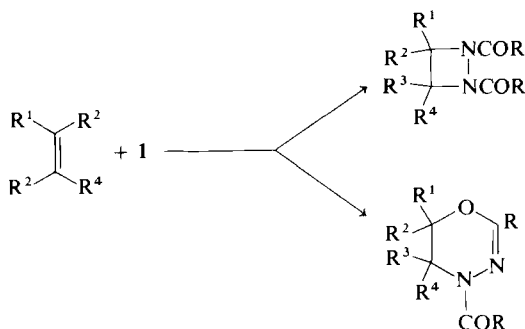
⁶⁵ E. J. Corey and B. B. Snider, *Tetrahedron Lett.*, 3091 (1973).

⁶⁶ R. Breslow, R. J. Corcoran, B. B. Snider, R. J. Doll, P. L. Khanna, and R. Kaleya, *J. Am. Chem. Soc.* **99**, 905 (1977).



In a comparative study, Jacobson *et al.* have shown that for the *cis*-fused cyclohexadiene, 1,2,3,4,4a,8a-hexahydronaphthalene, the dienophilic reactivity follows the order PTAD > *cis*-DEAZD > *trans*-DEAZD, while the order is reversed for their reactivity as enophiles.⁶⁷ Other studies have produced similar conclusions.^{21,54} In general, azo compounds give more ene product than the corresponding C=C compounds.

Olefins which do not contain an allylic hydrogen atom, and therefore cannot enter into the ene reaction, nevertheless usually react with ADC compounds. Two modes of reaction are possible for acyclic ADC compounds: 1,2-addition to give a 1,2-diazetidine, and 1,4-addition, with the ADC compound acting as a 4 π component, to give a 1,3,4-oxadiazine derivative as shown in Scheme 1. Both types of reaction have been observed, some olefins giving a single product, while others give mixtures of 1,2- and 1,4-addition products. Electron-rich olefins such as tetramethoxyethene give exclusively the 1,2-diazetidine with DEAZD.⁶⁸ Indene and 1,2-dimethoxyethene give predominantly 1,4-addition, *cis*-DEAZD reacting considerably faster than the *trans* form.⁶⁹ (The mechanistic aspects of this reaction are discussed in Section IV,B.) Acyclic ADC compounds also act as



SCHEME 1

⁶⁷ B. M. Jacobson, A. C. Feldstein, and J. I. Smallwood, *J. Org. Chem.* **42**, 2849 (1977).

⁶⁸ R. W. Hoffmann, U. Bressel, J. Gehlhaus, and H. Häuser, *Chem. Ber.* **104**, 873 (1971).

⁶⁹ E. K. von Gustorf, D. V. White, B. Kim, D. Hess, and J. Leitich, *J. Org. Chem.* **35**, 1155 (1970).

formal 4π components in their reactions with carbenes (see Section IV,C). Cyclic ADC compounds are sterically constrained and can only add in a 1,2 fashion. 1,2-Diazetidines have been isolated from the reaction of indene with PTAD,⁶⁹ and phthalazine-1,4-dione.⁷⁰

C. REACTION WITH 1,3-DIPOLES

As might be expected of a reactive dienophile, ADC compounds react readily with a variety of 1,3-dipoles to give five-membered ring heterocycles. These reactions are discussed in detail in Section IV,C.

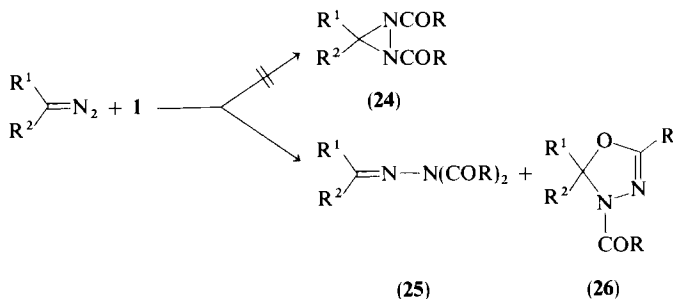
D. REACTION WITH NUCLEOPHILES

The nitrogen atoms in ADC compounds are highly electrophilic. Nucleophilic attack on nitrogen is easy, and as with "electrophilic" acetylenes, such as dimethyl acetylenedicarboxylate, it seems likely that some cycloaddition reactions of ADC compounds with unsymmetrical substrates proceed via a stepwise mechanism. PTAD is a powerful electrophile, although TCNE is more reactive, and chlorosulfonyl isocyanate is more reactive still.⁵⁸

IV. Use of Azodicarbonyl Compounds in Heterocyclic Synthesis

A. PREPARATION OF THREE-MEMBERED RINGS

By analogy with cyclopropane formation from carbenes and $C=C$ bonds, azo compounds might be expected to give diaziridines in their reaction with carbenes. Although acyclic ADC compounds react readily with diazoalkanes

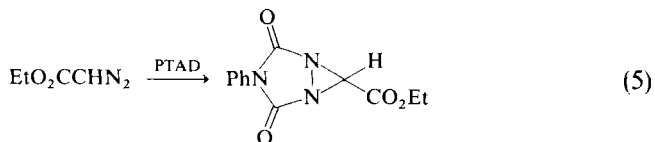


SCHEME 2

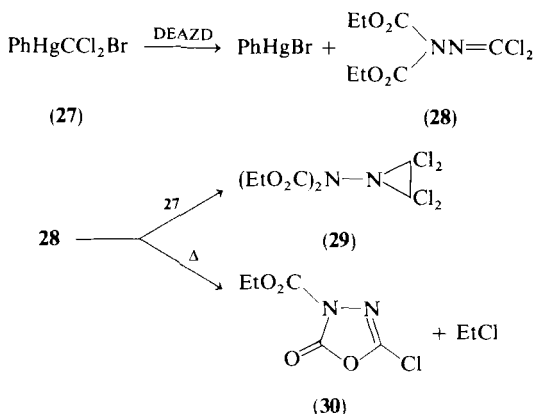
⁷⁰ O. L. Chapman and S. J. Dominianni, *J. Org. Chem.* **31**, 3862 (1966).

and diazoacetic esters to liberate nitrogen, the products are not the expected diaziridines **24** resulting from 1,2-addition of the "carbene" across the $\text{N}=\text{N}$ bond, but either hydrazones **25**, or 1,3,4-oxadiazolines **26** (Scheme 2). The mechanism of oxadiazoline formation, formally the 1,4-addition of the carbene across the $-\text{N}=\text{N}-\text{C}=\text{O}$ system acting as a 4π component, is discussed in Fahr's review.¹

When the possibility of 1,4-addition is precluded by incorporation of the $-\text{N}=\text{N}-\text{C}=\text{O}$ system into a ring, then 1,2-addition of the carbene should be possible. However, only one example has so far been reported. Ethyl diazoacetate reacts exothermically with PTAD at 0°C to liberate nitrogen and give a 1:1 adduct which was assigned the diaziridine structure shown in Eq. (5).⁷¹



Dichlorocarbene, thermally generated from the organomercury compound (**27**), gave a 1:1 adduct with DEAZD, which probably has the phosgene hydrazone structure (**28**). Further reaction with dichlorocarbene does give a three-membered ring, the aziridine **29**, and on heating, **28** rearranges to the 1,3,4-oxadiazol-2-one (**30**) (Scheme 3).⁷² An analogous hydrazone structure, $(\text{EtO}_2\text{C})_2\text{N}-\text{N}=\text{C}(\text{CN})_2$ has been proposed for the product of the reaction of DEAZD and dicyanocarbene.⁷³



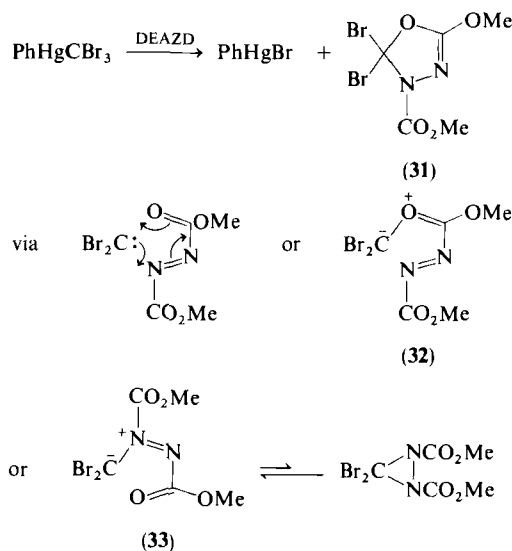
SCHEME 3

⁷¹ R. A. Izydore and S. McLean, *J. Am. Chem. Soc.* **97**, 5611 (1975).

⁷² D. Seyferth and H. Shih, *J. Org. Chem.* **39**, 2329 (1974).

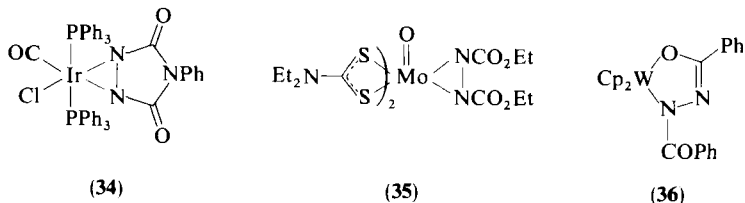
⁷³ E. Ciganek, *J. Am. Chem. Soc.* **88**, 1979 (1966).

In the analogous reaction of dibromocarbene with DMAZD, an intermediate was isolated. The compound was assigned the 1,3,4-oxadiazoline structure **31** on the basis of ^{13}C NMR. This can be envisaged as arising from concerted 1,4-addition of dibromocarbene to DMAZD, or by initial electrophilic attack of the carbene on oxygen to give **32**. Alternatively, electrophilic attack on nitrogen would lead to intermediate **33**. Equilibration of **33** with the diaziridine cannot be ruled out (Scheme 4). Oxadiazoline **31** rapidly rearranges on mild heating to give $(\text{MeO}_2\text{C})_2\text{N}-\text{N}=\text{CBr}_2$.⁷²



SCHEME 4

Certain transition metal complexes may act like carbenes, and give three-membered metallocycles with ADC compounds.⁷⁴ For example, complexes **34** and **35** are readily formed. The carbene analogy also extends to the formation of 1,4-addition products (e.g., **36**)⁷⁵



⁷⁴ M. Green, R. B. L. Osborn and F. G. A. Stone, *J. Chem. Soc. A*, 3083 (1968); P. W. Schneider, D. C. Bravard, J. W. McDonald, and W. E. Newton, *J. Am. Chem. Soc.* **94**, 8640 (1972); L. S. Liebeskind, K. B. Sharpless, R. D. Wilson, and J. Albers, *ibid.* **100**, 7061 (1978).

⁷⁵ A. Nakamura, M. Aotake, and S. Otsuka, *J. Am. Chem. Soc.* **96**, 3456 (1974).

The decomposition of azides in the presence of ADC compounds has been studied.⁷⁶ Addition of a nitrene across the $N=N$ group has not been observed, and although triaziridines have been proposed, the structures are probably incorrect. The reaction deserves further study (see also Section V,C).

B. PREPARATION OF FOUR-MEMBERED RINGS

The use of the ADC $N=N$ bond as a 2π component in $[2 + 2]$ cycloaddition reactions should lead to four-membered rings, and indeed the reaction of ADC compounds with carbon-carbon double bonds is a useful preparative route to the relatively rare 1,2-diazetidines, which despite its simplicity is not readily accessible. DEAZD reacts with ethylene, and with fluoroolefins under conditions of high temperature and pressure to give the expected 1,2-diazetidines.^{77,78} The 1,2-diazetidines structure **37** was previously assigned to the adduct from indene and DEAZD.⁷⁹ Subsequent work has shown that the adduct has the alternative oxadiazine structure **38**.⁸⁰ Similar confusion has arisen over the structure of the adducts from norbornadiene and ADC compounds. In addition to the expected homoconjugate Diels-Alder product **39**, a second product was isolated.⁸¹ This was variously assigned the *endo*-1,2-diazetidines structure (**40**, $R = OEt$) or the structure **41**, but in fact has the oxadiazine structure **42**.⁸² However, *exo*-1,2-diazetidines (**40**, $R = Ar$) are formed in good yield from the reaction of azodiaroyls with quadricyclane.⁸³ Structures of type **41** are formed from benzonorbornadiene and ADC compounds (see Section IV,D,3).

⁷⁶ T. Curtius and W. Sieber, *J. Prakt. Chem.* **125**, 444 (1930); M. Colonna and A. Risalti, *Gazz. Chim. Ital.* **91**, 204 (1961); J. Hancock, *Tetrahedron Lett.*, 1585 (1964); W. Lwowski, T. W. Mattingly, and T. K. Maricich, *ibid.*, 1591.

⁷⁷ M. A. Englin, A. S. Filatov, and N. F. Sirotenkova, *J. Org. Chem. USSR (Engl. Transl.)* **5**, 1555 (1969).

⁷⁸ R. D. Cramer, U. S. Patent 2,456,176 (1948); J. C. Kauer and A. K. Schneider, *J. Am. Chem. Soc.* **82**, 852 (1960); S. A. Rodkin, A. Y. Yakubovich, and S. P. Makarov, *J. Org. Chem. USSR (Engl. Transl.)* **7**, 2361 (1971).

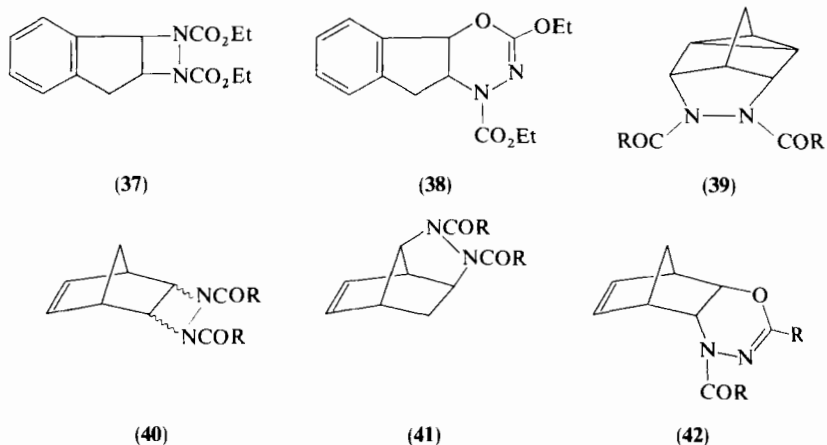
⁷⁹ E. K. von Gustorf and B. Kim, *Angew. Chem.* **76**, 592 (1964); C. F. Huebner, P. L. Strachan, E. M. Donoghue, N. Cahoon, L. Dorfman, R. Margerison, and E. Wenkert, *J. Org. Chem.* **32**, 1126 (1967).

⁸⁰ C. F. Huebner, E. M. Donoghue, C. J. Novak, L. Dorfman, and E. Wenkert, *J. Org. Chem.* **35**, 1149 (1970).

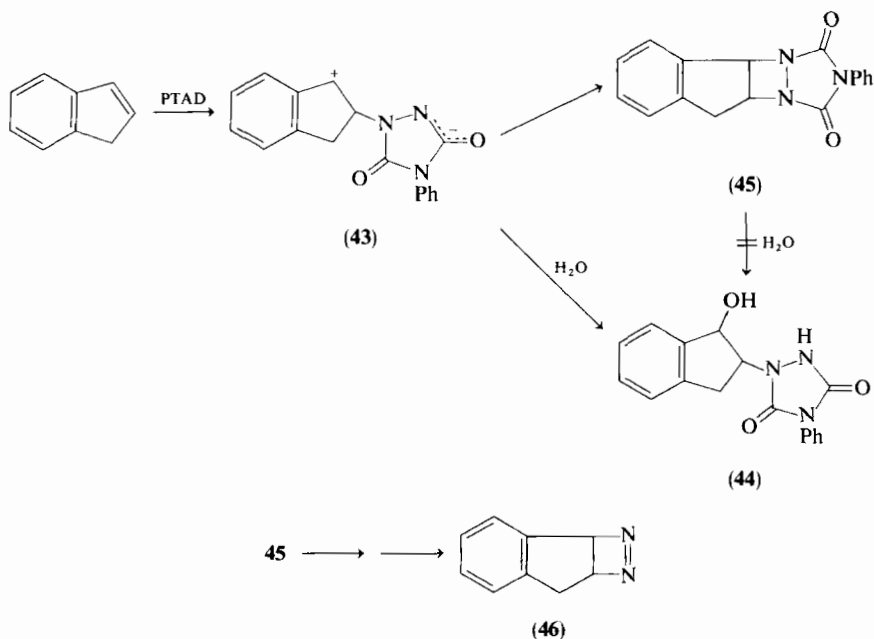
⁸¹ R. M. Moriarty, *J. Org. Chem.* **28**, 2385 (1963); S. J. Cristol, E. L. Allred, and D. L. Wetzel, *ibid.* **27**, 4058 (1962).

⁸² J. L. Tufariello, T. F. Mich, and P. S. Miller, *Tetrahedron Lett.*, 2293 (1966).

⁸³ M. E. Landis and J. C. Mitchell, *J. Org. Chem.* **44**, 2288 (1979).



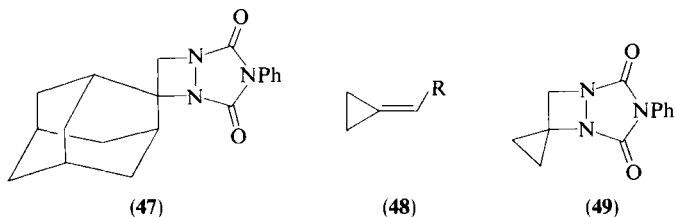
Indene, however, does give four-membered ring adducts with PTAD,⁶⁹ and phthalazine-1,4-dione.⁷⁰ The reaction with PTAD proceeds stepwise via the dipolar intermediate **43**, which was trapped in the presence of water to give **44**, under conditions in which the 1,2-diazetidine (**45**) was not opened by water to **44** (Scheme 5).⁶⁹ Hydrolytic cleavage of the triazole ring in **45** using potassium *tert*-butoxide in wet dimethyl sulfoxide, followed by



SCHEME 5

oxidation with copper(II) chloride gave the four-membered ring azo compound **46**.⁸⁴

Carbocyclic compounds containing an unsubstituted exocyclic methylene group give 1,2-diazetidines with PTAD. Methylene adamantane gives the adduct **47**,⁸⁵ and the methylene cyclopropane (**48**, R = H) gave the 1,2-diazetidine **49**.⁸⁶ The phenyl-substituted compound (**48**, R = Ph) behaved similarly to styrene and gave a 2:1 adduct with PTAD (see Section IV,D,1).



A 1,2-diazetidine has been proposed as an intermediate in the reaction of pyridazine-3,6-dione (**12**) with styrene.⁸⁷ The observed product was thought to arise from addition of water to the 1,2-diazetidine, although the alternative more likely explanation involving a dipolar intermediate (cf. Scheme 5) was apparently not considered. In the photochemical reaction of styrene with DEAZD, a 1,2-diazetidine structure was tentatively assigned to a minor product.⁸⁸ Attempted photochemical [2 + 2] cycloaddition of DEAZD to other olefins failed to give any 1,2-diazetidines.⁸⁸

Although highly electron-rich (nucleophilic) olefins such as tetramethoxyethene give preparatively useful yields of 1,2-diazetidines with ADC compounds,⁶⁸ possibly via stepwise addition to the electrophilic N=C=O system, the reaction is highly sensitive to changes in substituents, and the competing 1,4-addition to give 1,3,4-oxadiazines may supervene (Scheme 1). In a series of papers, Firl and Sommer have reported investigation of the reaction of various unsymmetrical electron-rich olefins (e.g., enol ethers and enamines) with acyclic ADC compounds. They found that for the reaction of DMAZD with the olefins **50**, the yield of 1,2-diazetidine (**51**, R = OMe) increased with the donor ability of the substituent X (X = 9-carbazolyl, SET, OEt, OAc).⁸⁹ The yields of diazetidine were reasonable (62–87%) with none of the 1,4-addition product **52** (R = OMe) being detected. However, in the series of aryl vinyl ethers (**50**, X = 4-Y—C₆H₄O) the ratio of **51**:**52** (R = OMe) varied from 87:13 for Y = OMe to <5:>95 for Y = NO₂.⁹⁰ The

⁸⁴ J. A. Pincock and L. M. Druet, *Tetrahedron Lett.*, 3251 (1980).

⁸⁵ T. Sasaki, S. Eguchi, and Y. Hirako, *Tetrahedron* **32**, 437 (1976).

⁸⁶ D. J. Pasto and A. F.-T. Chen, *Tetrahedron Lett.*, 2995 (1972); 713 (1973).

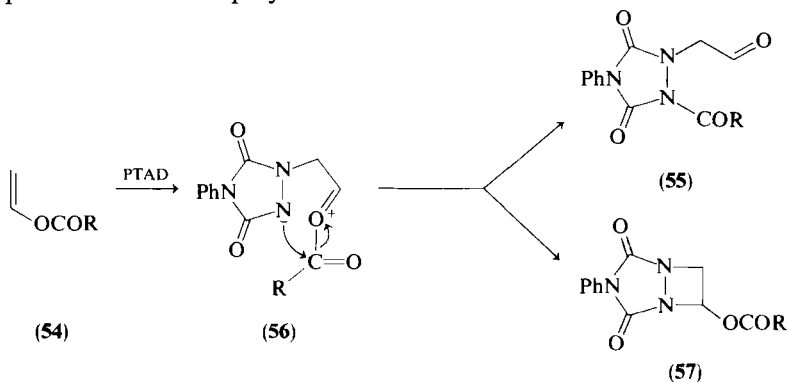
⁸⁷ M. Lora-Tamayo, P. Navarro, and J. L. Soto, *Justus Liebigs Ann. Chem.* **748**, 96 (1971).

⁸⁸ G. Ahlgren, and B. Akermarck, *Acta Chem. Scand.* **21**, 2910 (1967).

⁸⁹ J. Firl and S. Sommer, *Tetrahedron Lett.*, 1133 (1969).

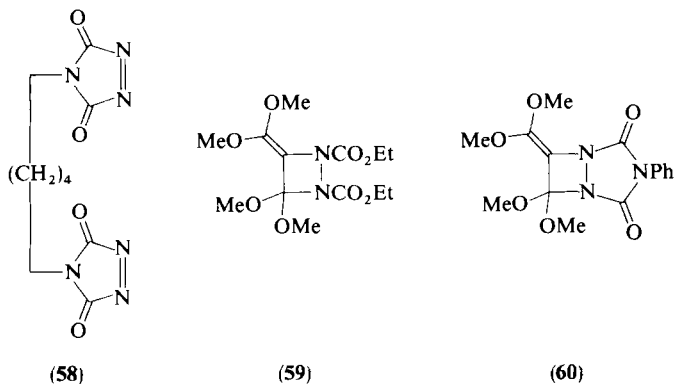
⁹⁰ J. Firl and S. Sommer, *Tetrahedron Lett.*, 1929 (1970).

tert-butyl ester (**54**, R = *t*-Bu) was used, intramolecular attack on the carbonyl group in **56** was sterically hindered, and the dipole collapsed to the 1,2-diazetidine (**57**, R = *t*-Bu) as shown in Scheme 6. Additional kinetic evidence further supports the dipolar intermediates,⁹⁷ and the reaction has been extended by using bis-1,2,4-triazole-3,5-diones (e.g., **58**) with divinyl adipate to make novel polymers.⁹⁸



SCHEME 6

ADC compounds add to allenes to give 3-methylene-1,2-diazetidines. Tetramethoxyallene adds to DEAZD and to PTAD to give adducts **59** and **60** in 43 and 69% yield.⁹⁹ DEAZD adds to the 2,3-double bond of 1,1-difluoroallene (in poor yield), in contrast to maleic anhydride which adds to the 1,2-double bond.¹⁰⁰



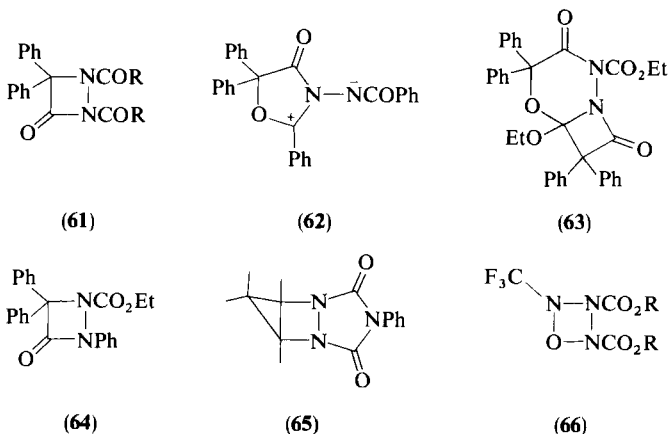
⁹⁷ K. B. Wagener and G. B. Butler, *J. Org. Chem.* **38**, 3070 (1973).

⁹⁸ K. A. Matyjaszewski, K. B. Wagener, and G. B. Butler, *J. Polym. Sci., Polym. Lett. Ed.* **17**, 65 (1979).

⁹⁹ R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **11**, 324 (1972).

¹⁰⁰ W. H. Knoth and D. D. Coffman, *J. Am. Chem. Soc.* **82**, 3873 (1960).

The reaction of ADC compounds with ketenes has been discussed.¹ The reaction is usually complex, but in certain cases, good yields of the formal [2 + 2] addition products, 1,2-diazetidines are claimed. Azodibenzoyl is reported to give the hydrolytically labile diazetidinone **61** (R = Ph) with diphenylketene.¹⁰¹ However, in more recent work, the azomethine imine structure **62** was assigned to the initial product of the reaction.¹⁰² The initial 2:1 adduct (**63**) from diphenylketene and DEAZD irreversibly loses diphenylketene on heating to give a compound which was assigned the diazetidinone structure **61** (R = OEt).¹⁰³ The related azomonocarbonyl compound, PhN=NCO₂Et, gives the diazetidinone **64** in 70% yield.^{104,105} Ketene acetals give the products of 1,4- rather than 1,2-addition on reaction with ADC compounds.¹⁰⁶



Addition of PTAD to 3,4,4,5-tetramethyl-4H-pyrazole gave the expected Diels-Alder adduct, which on photolysis gave the condensed diazetidine **65** in good yield.¹⁰⁷ The unlikely four-membered ring structure **66** has been assigned to the product from azodicarboxylates and trifluoronitrosomethane.¹⁰⁸

¹⁰¹ L. Horner and E. Spietschka, *Chem. Ber.* **89**, 2765 (1956).

¹⁰² J. Markert and E. Fahr, *Tetrahedron Lett.*, 769 (1970).

¹⁰³ E. Fahr, K. H. Keil, F. Scheckenbach, and A. Jung, *Angew. Chem., Int. Ed. Engl.* **3**, 646 (1964).

¹⁰⁴ C. W. Bird, *J. Chem. Soc.*, 674 (1963).

¹⁰⁵ R. C. Kerber, T. J. Ryan, and S. D. Hsu, *J. Org. Chem.* **39**, 1215 (1974).

¹⁰⁶ J. H. Hall and M. Wojciechowska, *J. Org. Chem.* **43**, 3348, 4869 (1978); **44**, 38 (1979).

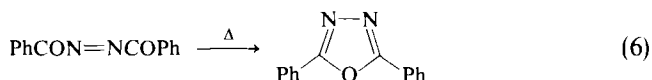
¹⁰⁷ A. B. Evnin, D. R. Arnold, L. A. Karnischky, and E. Strom, *J. Am. Chem. Soc.* **92**, 6218 (1970).

¹⁰⁸ S. P. Makarov, V. A. Shpanskii, V. A. Ginsburg, A. I. Shchekotikhin, A. S. Filatov, L. L. Martynova, I. V. Pavlovskaya, A. F. Golovaneva, and A. Y. Yabubovich, *Dokl. Akad. Nauk SSSR* **142**, 596 (1962) [*CA* **57**, 4527 (1962)].

C. PREPARATION OF FIVE-MEMBERED RINGS

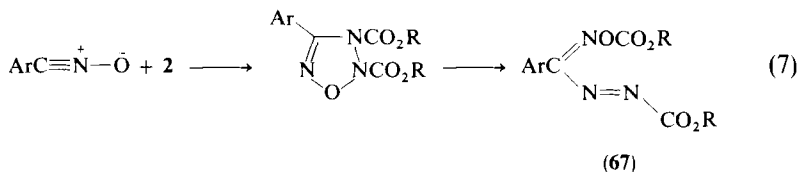
Five-membered ring heterocycles can be the result of cycloaddition reactions of ADC compounds acting as 2π components with 1,3-dipoles, or as 4π components in cheletropic reactions. They can also result from nucleophilic attack on the ADC compound, followed by ring closure of the initial adduct.

The thermal decomposition of some ADC compounds also gives five-membered rings. Thus, azodibenzoyl gives 2,5-diphenyl-1,3,4-oxadiazole (25%) on heating (Eq. 6),¹⁰⁹ probably via a mechanism involving attack of PhCO radical on undecomposed azodibenzoyl.¹¹⁰ The bismethylamide (1, R = MeNH) gave 4-methylurazole on heating.¹¹¹



1. Reaction with 1,3-Dipoles

Acyclic ADC compounds, in particular DEAZD, are often used as trapping agents for 1,3-dipoles. PTAD has been used less frequently, but seems equally effective. Aryl nitrile oxides add exothermically to DEAZD to give the labile 1,2,3,5-oxatriazoline ring system (Eq. 7).^{112,113} The ring system, which had not previously been prepared, readily rearranged via cleavage of the weak O—N₂ bond to give **67**.¹¹³



Photolysis of the azirines **68** in the presence of DEAZD gives 1,2,4-triazolines (**69**, R = Et) via cycloaddition to the nitrile ylid.¹¹⁴ The nitrile ylid generated thermally from **70** gives 1,2,4-triazolines (**69**, R = Me, R¹ = R² = CF₃) (Scheme 7).¹¹⁵ The cycloadditions proceed in good yield, and the triazolines **69** are readily converted into aromatic 1,2,4-triazoles.

¹⁰⁹ R. Stolle, *Chem. Ber.* **45**, 273 (1912).

¹¹⁰ D. Mackay, U. F. Marx, and W. A. Waters, *J. Chem. Soc.*, 4793 (1964).

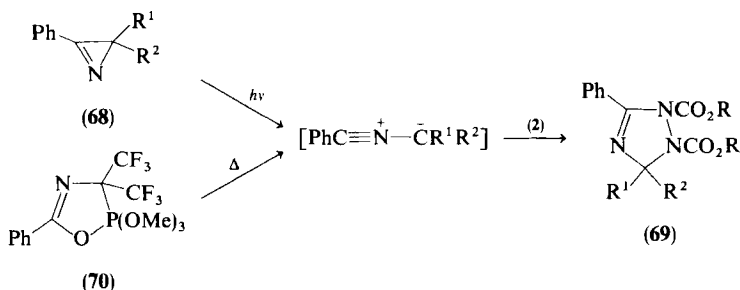
¹¹¹ R. F. Smith, S. B. Kaldor, E. P. Laganis, and R. F. Oot, *J. Org. Chem.* **40**, 1854 (1975).

¹¹² P. Rajagopalan, *Tetrahedron Lett.*, 887 (1964).

¹¹³ H. Blaschke, E. Brunn, R. Huisgen, and W. Mack, *Chem. Ber.* **105**, 2841 (1972).

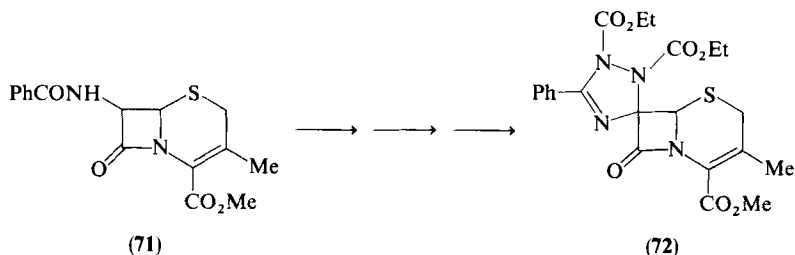
¹¹⁴ P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **57**, 1382 (1974).

¹¹⁵ K. Burger and K. Einhellig, *Chem. Ber.* **106**, 3421 (1973).

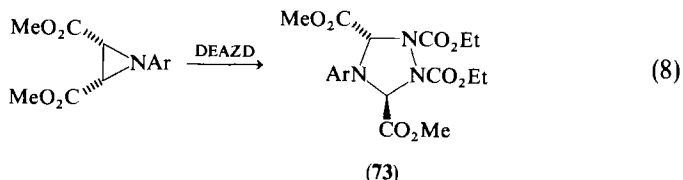


SCHEME 7

Conversion of cephalosporin **71** to the imidoyl chloride, followed by treatment with base in the presence of DEAZD gives a novel spiro β -lactam (**72**), again via nitrile ylid cycloaddition.¹¹⁶



1,2,4-Triazole derivatives also result from the cycloaddition of DEAZD to azomethine ylids derived from electrocyclic ring opening of aziridines.¹¹⁷⁻¹²¹ For example, the tetrahydro-1,2,4-triazole **73** was prepared by thermolysis of the *cis*-aziridine in the presence of DEAZD in 96% yield (Eq. 8), and



¹¹⁶ K. Hirai, Y. Iwano, Y. Saito, T. Hiraoka, and Y. Kishida, *Tetrahedron Lett.*, 1303 (1976).

¹¹⁷ E. Brunn and R. Huisgen, *Tetrahedron Lett.*, 473 (1971).

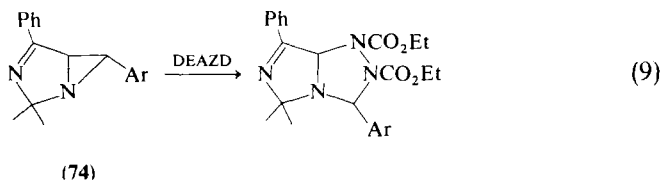
¹¹⁸ H. Duewelle, *Aust. J. Chem.* **30**, 1367 (1977).

¹¹⁹ H. W. Heine, R. Peavy, and A. J. Durbetaki, *J. Org. Chem.* **31**, 3924 (1966).

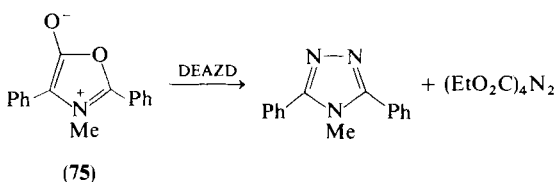
¹²⁰ H. W. Heine, A. B. Smith, and J. D. Bower, *J. Org. Chem.* **33**, 1097 (1968).

¹²¹ H. W. Heine and R. P. Henzel, *J. Org. Chem.* **34**, 171 (1969); H. W. Heine, T. A. Newton, G. J. Blossick, K. C. Irving, C. Meyer, and G. B. Corcoran, *ibid.* **38**, 651 (1973).

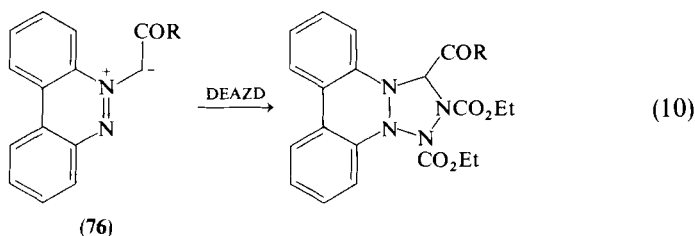
treating the aziridine **74** in xylene gave a triazoloimidazole derivative (76%) as shown in Eq. (9).^{117,120}



Benzylidenebenzylamine reacts with DEAZD, presumably via its azomethine ylid tautomer, to give the expected 3,5-diphenyl-1,2-diethoxycarbonyl-1,2,4-triazoline.¹²² The masked azomethine ylid **75** reacts with DEAZD with loss of CO₂ at 0°C. The initial adduct was not isolated, but reacted further with DEAZD to transfer ethoxycarbonyl groups giving 3,5-diphenyl-4-methyl-1,2,4-triazole (86%) and tetraethoxycarbonylhydrazine (89%).¹²³ The same triazole is formed in the reaction of **75** with azodibenzoyl (73%), and with PTAD (30%).



The benzocinnolinium azomethine imines **76** (R = Ph, OEt) react readily with DEAZD by 1,3-dipolar cycloaddition to give the corresponding tetrazolidine derivatives (Eq. 10).¹²⁴ The masked azomethine imine **77** is particularly unreactive as a 1,3-dipole, although PTAD reacts cleanly where other dipolarophiles either failed to react or gave complex mixtures (Eq. 11).¹²⁵

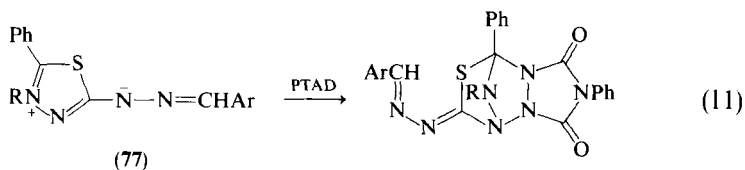


¹²² R. Grigg, J. Kemp, G. Sheldrick, and J. Trotter, *J. C. S. Chem. Commun.*, 109 (1978).

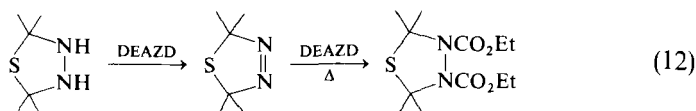
¹²³ E. Brunn, E. Funke, H. Gotthardt, and R. Huisgen, *Chem. Ber.* **104**, 1562 (1971).

¹²⁴ E. Carp, M. Dorneanu, and I. Zugravescu, *Rev. Roum. Chim.* **19**, 1507 (1974); **21**, 1203 (1976).

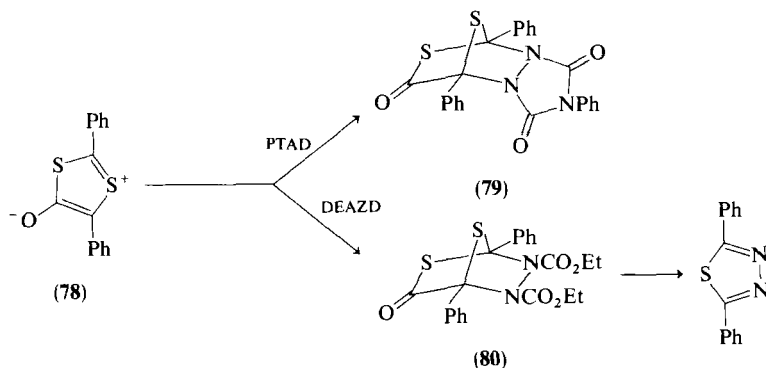
¹²⁵ E. Cawkill, W. D. Ollis, C. A. Ramsden, and G. P. Rowson, *J. C. S. Perkin Trans. I*, 724 (1979).



1,3,4-Thiadiazolidines are readily dehydrogenated by DEAZD. The resulting Δ^3 -1,3,4-thiadiazolines lose N_2 on heating to generate thiocarbonyl ylids, which can be intercepted by DEAZD to give 1,3,4-thiadiazolidines (Eq. 12); in the absence of DEAZD thiiranes and/or olefins result.^{126,127} Carbonyl ylids, generated by ring opening of epoxides, react similarly with DEAZD, although the initial adducts are often labile.¹²⁸



The mesoionic compound **78** adds to both PTAD and DEAZD as a 1,3-dipole to give **79** and **80**, respectively, in high yield. The DEAZD adduct can be converted into 2,5-diphenyl-1,3,4-thiadiazole (Scheme 8).¹²⁹



SCHEME 8

PTAD reacts readily at room temperature with vinyl azides to give products formally derived from 1,3-dipolar cycloaddition of an intermediate

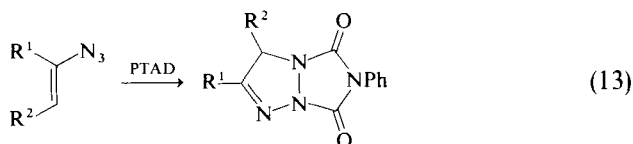
¹²⁶ J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.* **37**, 4045 (1972); R. M. Kellogg, M. Noteboom, and J. K. Kaiser, *Tetrahedron* **32**, 1641 (1976).

¹²⁷ T. Sasaki, S. Eguchi, and Y. Hirako, *Heterocycles* **4**, 1901 (1976).

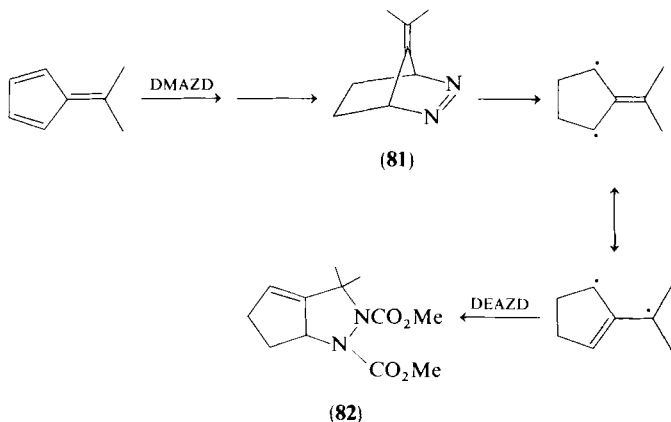
¹²⁸ H. Hamberger, R. Huisgen, V. Markowski, and S. Sustmann, *Heterocycles* **5**, 147 (1976).

¹²⁹ H. Gotthardt and C. M. Weissshuhn, *Chem. Ber.* **111**, 3171 (1978).

vinyl nitrene as shown in Eq. (13).¹³⁰ No addition of the azide 1,3-dipolar system to the N=N bond was observed.

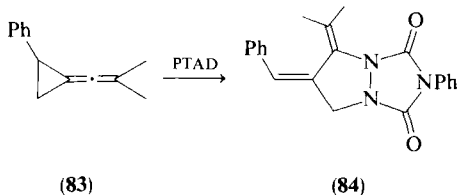


DMAZD also proved an effective trapping agent for the 1,3-diradical intermediate derived by thermal extrusion of N₂ from **81**, which was itself prepared from DMAZD and 6,6-dimethylfulvene (Scheme 9). The final product was the cyclopentapyrazole **82**.¹³¹



SCHEME 9

The reaction of PTAD with allenic cyclopropanes **83** gives high yields of the pyrazolotriazoles **84**.¹³² The reaction has been extensively studied, and



¹³⁰ A. Hassner, D. Tang, and J. Keogh, *J. Org. Chem.* **41**, 2102 (1976).

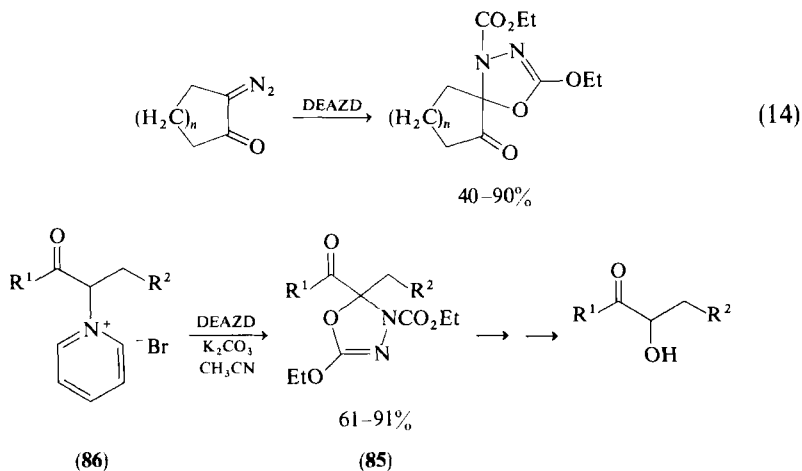
¹³¹ J. A. Berson, D. M. McDaniel, L. R. Corwin, and J. H. Davis, *J. Am. Chem. Soc.* **94**, 5508 (1972).

¹³² D. J. Pasto, A. F.-T. Chen, and G. Binsch, *J. Am. Chem. Soc.* **95**, 1553 (1973); D. J. Pasto and J. K. Borchardt, *ibid.* **96**, 6944 (1974).

diradicals are not involved. The mechanism is thought to involve an 8π electron process involving both allene double bonds; cf. the reaction of methylene cyclopropanes with PTAD which gives diazetidines.⁸⁶

2. Reaction with Carbenes

The reaction of ADC compounds with "carbenes" and their precursors has already been discussed in Section IV.A. In general, the heterocyclic products are not the result of 1,2-addition but of 1,4-addition of the carbene to the —N=N—C=O system.¹ Thus the ADC compound reacts as a 4π unit in a cheletropic reaction leading to the formation of 1,3,4-oxadiazolines. Recent applications include the preparation of spiro-1,3,4-oxadiazolines from cyclic diazoketones and DEAZD as shown in Eq. (14),¹³³ and the synthesis of the acyl derivatives **85** from the pyridinium salts **86**.¹³⁴ The acyl derivatives **85** are readily converted into α -hydroxyketones by a sequence of hydrolysis and reduction reactions.

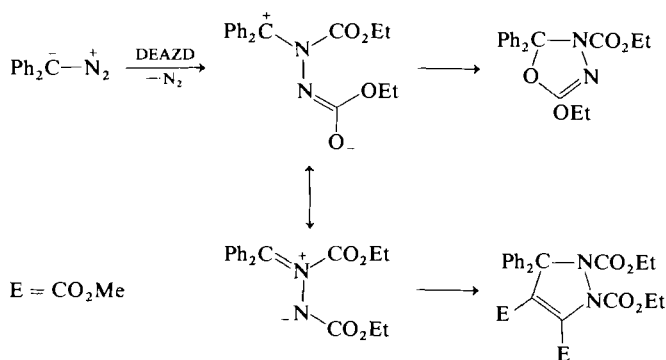


Although formally the product of 1,4-addition of the carbene to the ADC 4π unit, 1,3,4-oxadiazolines probably arise via initial nucleophilic attack of the diazo compound to give, after loss of N_2 , a dipolar intermediate. This intermediate azomethine imine can collapse directly to give the oxadiazoline,

¹³³ L. L. Rodina, I. K. Korobitsyna, and A. N. Osman, *Chem. Heterocycl. Compd. (Engl. Transl.)* **10**, 1494 (1974); L. L. Rodina, A. G. Osman, and I. K. Korobitsyna, *J. Org. Chem. USSR (Engl. Transl.)* **14**, 566 (1978).

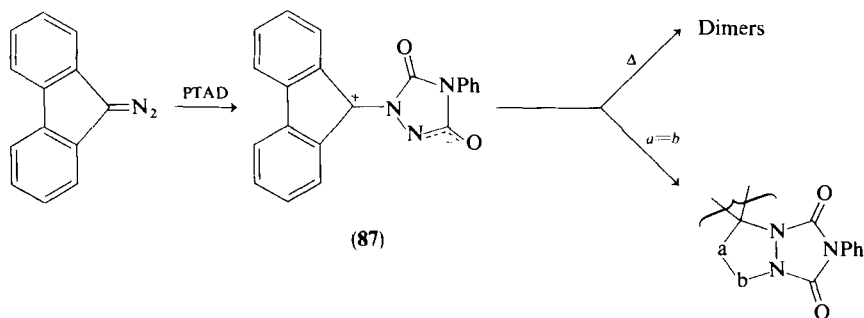
¹³⁴ T. Mukaiyama, K. Atsumi, and T. Takeda, *Chem. Lett.*, 597 (1976); T. Takeda, M. Ueda, and T. Mukaiyama, *ibid.*, 245 (1977).

or be intercepted by an added dipolarophile such as dimethyl acetylenedicarboxylate (Scheme 10).¹³⁵



SCHEME 10

In the reaction of diazofluorene with PTAD the dipolar intermediate (87) is isolable.¹³⁶ Collapse to a five-membered ring is prevented by the steric constraints of the cyclic system, and although three-membered ring formation is possible, dimerization is the only process observed on heating. However, the dipole reacts with a variety of dipolarophiles ($a=b$, $\text{PhN}=\text{CO}$, $\text{MeO}_2\text{CC}\equiv\text{CCO}_2\text{Me}$, etc.) to give the expected adducts as shown in Scheme 11.



SCHEME 11

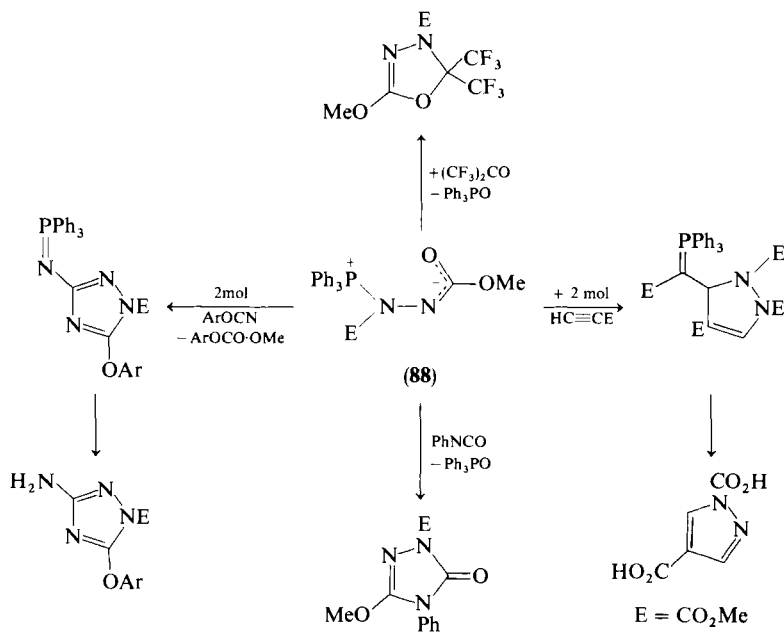
3. Reaction with Nucleophiles

Triphenylphosphine reacts readily with azodicarboxylates to give a dipolar intermediate, interception of which by dipolarophiles leads to a

¹³⁵ G. F. Bettinetti and P. Grunanger, *Tetrahedron Lett.*, 2553 (1965).

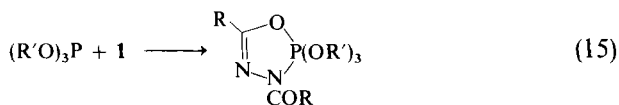
¹³⁶ W. Ried and S.-H. Lim, *Justus Liebigs Ann. Chem.*, 1141 (1973).

variety of heterocyclic systems in high yield. The reaction was originally thought to involve attack by the phosphine at one of the carbonyl oxygen atoms of the ADC compound,¹³⁷ but it seems much more likely that attack at the electrophilic nitrogen is the initial step leading to an intermediate with structure **88**. The interception of **88**, and consequent use in heterocyclic synthesis are summarized in Scheme 12 ($E = \text{CO}_2\text{Me}$).¹³⁸



SCHEME 12

Phosphites, however, undergo a cheletropic reaction with acyclic ADC compounds to give 1,2,3,4-oxaphosphadiazoles (Eq. 15).¹³⁹ Thiophosphites react similarly.¹⁴⁰



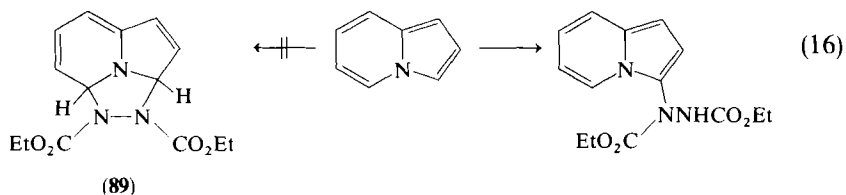
¹³⁷ R. C. Cookson and J. M. Locke, *J. Chem. Soc.*, 6062 (1963).

¹³⁸ E. Brunn and R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **8**, 513 (1969).

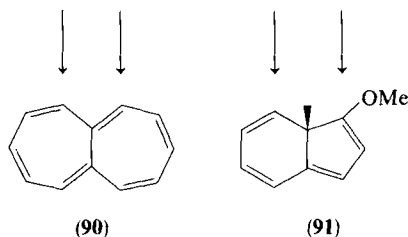
¹³⁹ V. A. Ginsburg, M. N. Vasil'eva, S. S. Dubov, and A. Y. Yakubovich, *J. Gen. Chem. USSR (Engl. Transl.)* **30**, 2834 (1960); B. A. Arbusov, *Khim. Primen. Fosfororg. Soedin, Tr. Konf.* **4th**, 1969, 43 (1972) [*CA* **78**, 136377 (1973)]; J. Navech, R. Kraemer, and J.-P. Majoral, *Tetrahedron Lett.*, 1449 (1980).

¹⁴⁰ J.-P. Majoral, R. Kraemer, T. N. M'Pondo, and J. Navech, *Tetrahedron Lett.*, 1307 (1980).

Electron-rich heterocyclic systems such as indolizines react readily with DEAZD (and PTAD) to give substitution products (Eq. 16).¹⁴¹ None of the formal $[8 + 2]$ cycloaddition products (e.g., **89**) are observed. This is in direct contrast to the reaction of indolizines with electrophilic acetylenes which gives high yields of cycloaddition products, presumably via a stepwise mechanism, in the presence of palladium on charcoal.¹⁴² This example of



an electrophilic ADC compound giving substitution products with electron-rich (nucleophilic) heterocycles when electrophilic acetylenes give cycloaddition products is by no means an isolated one; it has been observed in other systems. For example, 2-methylnaphtho[1,8-*de*]triazine,¹⁴³ isoindoles and related compounds¹⁴⁴ give only substitution products with DEAZD, but cycloaddition products with acetylenedicarboxylates. Thus, although azodicarboxylates are generally better dienophiles than the corresponding acetylenes, with certain substrates the more potent electrophilic properties of the ADC compound tend to dominate the situation. The electron-rich carbocyclic compounds heptalene (**90**)¹⁴⁵ and the novel 3a*H*-indene (**91**)¹⁴⁶ both give "cycloaddition" products with PTAD.



¹⁴¹ M. Colonna, P. Bruni, and A. Monti, *Gazz. Chim. Ital.* **94**, 509 (1964); C. M. Gupta, R. K. Rizvi, and N. Anand, *Indian J. Chem., Sect. B* **14B**, 57 (1976); M. Masumura and Y. Yamashita, *Heterocycles* **12**, 787 (1979).

¹⁴² R. M. Acheson, and N. F. Elmore, *Adv. Heterocycl. Chem.* **23**, 263 (1978).

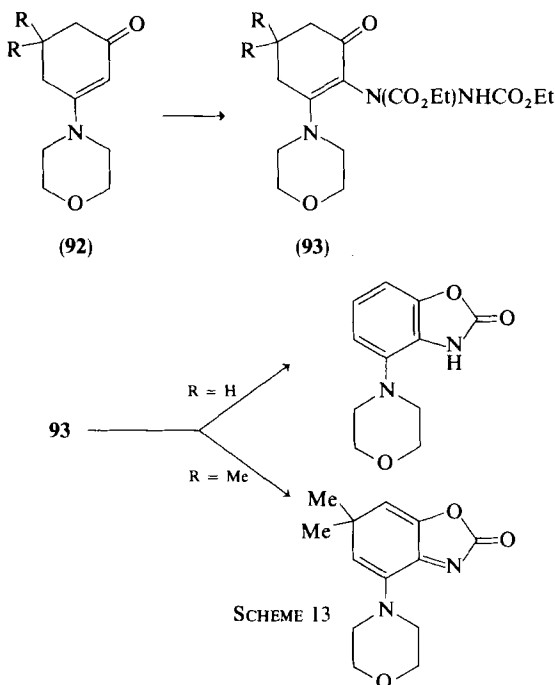
¹⁴³ S. F. Gait, M. J. Rance, C. W. Rees, R. W. Stephenson, and R. C. Storr, *J. C. S. Perkin I*, 556 (1975).

¹⁴⁴ R. Kreher and K. J. Herd, *Tetrahedron Lett.*, 1661 (1976); R. Kreher and G. Use, *ibid.*, 4671 (1978); R. Kreher, D. Schmitt, and K. J. Herd, *ibid.*, 3471 (1980).

¹⁴⁵ L. A. Paquette, A. R. Browne, and E. Chamot, *Angew. Chem., Int. Ed. Engl.* **18**, 546 (1979).

¹⁴⁶ T. L. Gilchrist, C. W. Rees, and D. Tuddenham, *J. C. S. Chem. Commun.*, 689 (1980).

Synthetic use can be made of the potent electrophilic properties of ADC compounds by transforming the initial adducts into heterocyclic products. For example, reaction of DEAZD with enamine **92** gives the substitution product **93** in quantitative yield. Further treatment of this initial adduct with acid, followed by base hydrolysis leads to benzoxazol-2-ones. The dimethyl substituted enamine (**92**, R = Me) gives the rare, but isolable 6*H*-benzoxazol-2-one ring system (Scheme 13).¹⁴⁷



A novel approach to purine synthesis involves the use of ADC compounds as a source of one nitrogen atom in the five-membered ring.^{148–150} Treatment of 6-amino-1,3-dimethyluracil (**94**, R = H) with DEAZD gives the 5-substitution product (**95**, R = H). The N—N bond is cleaved by Raney nickel or formic acid, and ring closure to 1,3-dimethyluric acid is simply effected by heating.¹⁴⁸ Whether the initial adduct is formed by a substitution

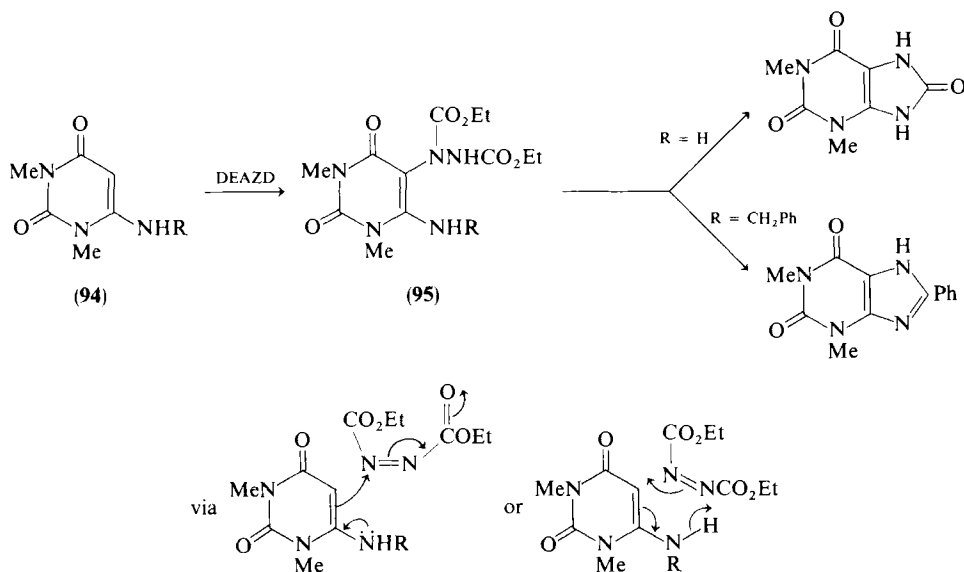
¹⁴⁷ F. P. Colonna, G. Pitacco, and E. Valentin, *J. C. S. Chem. Commun.*, 71 (1975).

¹⁴⁸ E. C. Taylor and F. Sowinski, *J. Org. Chem.* **39**, 907 (1974).

¹⁴⁹ F. Yoneda, M. Higuchi, and S. Matsumoto, *J. C. S. Perkin I*, 1754 (1977).

¹⁵⁰ F. Yoneda, M. Kawamura, S. Matsumoto, and M. Higuchi, *J. C. S. Perkin I*, 2285 (1977).

reaction or by an ene reaction is not known (Scheme 14). The 6-benzylamino derivative (**95**, $R = CH_2Ph$) cyclizes on treatment with more DEAZD to give 8-phenyltheophylline in high yield.¹⁴⁹ The theophylline is also formed directly from the uracil (**94**, $R = CH_2Ph$) by treatment with excess DEAZD at 170°C; the excess DEAZD is presumably required for dehydrogenation. PTAD has also been used as the source of one nitrogen atom in purine synthesis.¹⁵⁰ A similar approach has been used for the synthesis of six-membered rings such as alloxazines; this is described in Section IV,D,4.

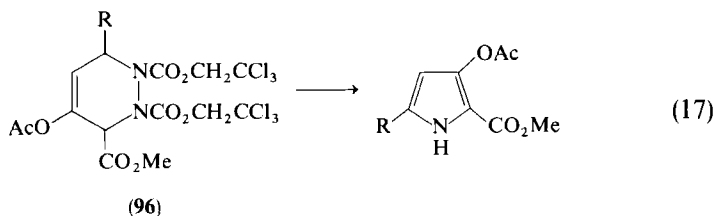


SCHEME 14

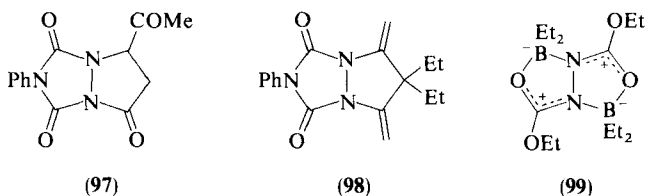
4. Miscellaneous

The concept of five-membered ring heterocyclic synthesis by transformation of the initial adduct of the ADC compound and substrate is not limited to cyclization of substitution products. 1,3,4-Oxadiazol-2-ones (**30**, Scheme 3) result from heating the initial DEAZD–dichlorocarbene adduct.⁷² Treatment of the Diels–Alder adducts **96** with zinc in acetic acid gives pyrroles in good yield (Eq. 17).¹⁵¹ The reaction has been extended to the synthesis of dipyrroles from the appropriate Diels–Alder adduct (**96**, $R =$ pyrrol-2-yl).

¹⁵¹ G. Kresze, M. Morper, and A. Bijev, *Tetrahedron Lett.*, 2259 (1977).



Reaction of PTAD with α -angelica lactone gives the pyrazolotriazole **97** via an acyl ene reaction,¹⁵² and reaction with 4,4-diethyl-3,5-dimethyl-4*H*-pyrazole 2-oxide gives **98** after heating.¹⁵³ A mesoionic bicyclic system **99** is proposed as a product from the reaction of DEAZD with triethylborane.¹⁵⁴



D. PREPARATION OF SIX-MEMBERED RINGS

As with five-membered ring formation, the reactions of ADC compounds which lead to six-membered ring heterocycles can be classified according to how the ADC compound reacts in the initial step. Most common is the Diels–Alder reaction, with the ADC compound acting as dienophile. Six-membered rings also result from the reaction of monoenes with ADC compounds acting as the 4π component, and by cyclization or other transformation of an initial adduct.

1. Reaction with Dienes

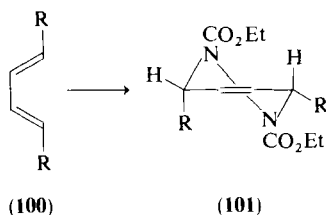
The Diels–Alder reaction is a useful way of synthesizing six-membered carbocyclic rings. Since ADC compounds are usually better dienophiles than the corresponding $C=C$ compounds, the Diels–Alder reaction provides a good general route to pyridazines, and their reduced derivatives. Although vast numbers of examples of Diels–Alder reaction involving ADC compounds have been reported, not many of these have been aimed specifically at heterocyclic synthesis.

¹⁵² W. E. Bottomley, G. V. Boyd, and R. L. Monteil, *J. C. S. Perkin I*, 843 (1980).

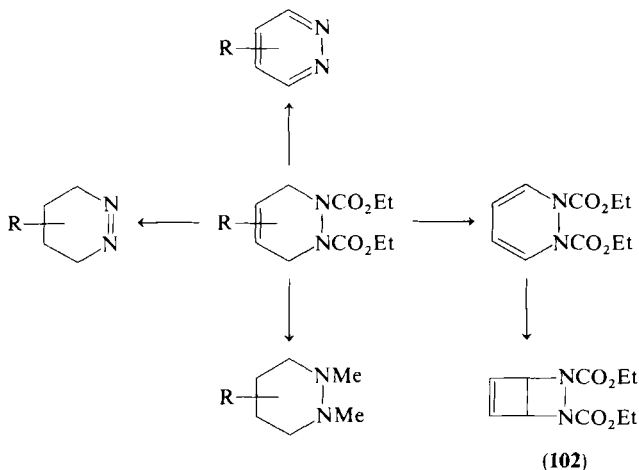
¹⁵³ W. R. Dolbier, W. D. Loehle, and W. M. Williams, *J. C. S. Chem. Commun.*, 867 (1972).

¹⁵⁴ A. Haag and H. Baudisch, *Tetrahedron Lett.*, 401 (1973).

The Diels–Alder reaction between DEAZD and 1,4-substituted butadienes occurs rapidly, and the adducts are obtained in high yield, retaining the initial configuration of the diene substituents in the product; i.e., diene **100** gives adduct **101** exclusively.¹⁵⁵ This is in accord with the expected concerted, stereospecific nature of the Diels–Alder reaction. These initial adducts



are readily converted into pyridazines and into reduced derivatives as shown in Scheme 15. Aromatic pyridazines are formed by a series of hydrolysis, decarboxylation, bromination, and dehydrobromination reactions.¹⁵⁶ Catalytic hydrogenation, followed by LiAlH₄ reduction gives 1,2-dimethylhexahydropyridazines,¹⁵⁷ and reaction with *N*-bromosuccinimide and 2,6-lutidine gives the 1,2-dihydropyridazine, a precursor for **102**.¹⁵⁸ Catalytic



SCHEME 15

¹⁵⁵ R. Daniels and K. A. Roseman, *Tetrahedron Lett.*, 1335 (1966).

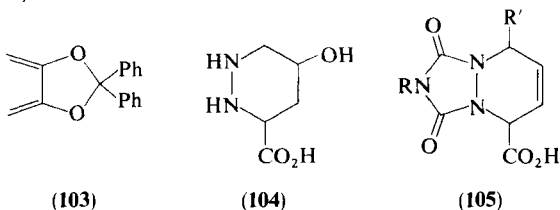
¹⁵⁶ P. Baranger and J. Levisalles, *Bull. Soc. Chim. Fr.*, 704 (1957).

¹⁵⁷ R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J. C. S. Perkin II*, 406 (1974).

¹⁵⁸ L. J. Altman, M. F. Semmelhack, R. B. Hornby, and J. C. Vederas, *J. C. S. Chem. Commun.*, 686 (1968); *Org. Prep. Proced. Int.* 7, 35 (1975).

reduction, hydrolysis, decarboxylation, and oxidation leads to cyclic azo compounds. This reaction is considered separately in Section IV.D.2.

4,5-Dihydroxypyridazines are readily prepared from the diene **103** and DEAZD or PTAD,¹⁵⁹ and the amino acid **104**, a constituent of the Monamycin antibiotics, was synthesized from the Diels–Alder adduct of phthalazine-1,4-dione and penta-2,4-dienoic acid.¹⁶⁰ These unusual amino acids can also be synthesized from the PTAD and parent HTAD adducts of penta-2,4-dienoic acid,¹⁶¹ and a variety of similar adducts, triazolo-pyridazines **105**, has been synthesized from a wide range of 4-substituted 1,2,4-triazole-3,5-diones.¹⁶²



Novel steroidal pyridazines are readily prepared from ADC compounds and steroidal $\Delta^{2,4}$ -dienes,¹⁶³ $\Delta^{14,16}$ -dienes,¹⁶⁴ and $\Delta^{16,20}$ -dienes.¹⁶⁵ ADC compounds are also commonly used in the protection of the steroid 5,7-diene system (see Section V,A). These Diels–Alder adducts of steroidal dienes and azo dienophiles should not be confused with the so-called azasteroids, which are also prepared from ADC compounds. Cyclic ADC compounds such as the pyrazole-3,5-diones (**7**), and the diazaquinones **12** and **13** readily add to dienes to give bicyclic pyridazine derivatives,^{166–168} and these reactions have been adapted to the synthesis of 5,10-diaza-steroids (**106**).⁴² Similarly, the 13,14-diaza- (**107**) and 13,14,16-triaza-steroid (**108**) ring systems have been prepared.¹⁶⁹

¹⁵⁹ G. M. Coppola and S. P. Gimelli, *J. Heterocycl. Chem.* **10**, 323 (1973).

¹⁶⁰ K. Bevan, J. S. Davies, C. H. Hassall, R. B. Morton, and D. A. S. Phillips, *J. Chem. Soc. C*, 514 (1971); C. H. Hassall and K. L. Ramachandran, *Heterocycles* **7**, 119 (1977).

¹⁶¹ C. R. Davies and J. S. Davies, *J. C. S. Perkin I*, 2390 (1976).

¹⁶² C. J. Moody and C. H. Hassall, European Patent Appl. 80104300.1 (1980).

¹⁶³ S. S. H. Gilani and D. J. Triggle, *J. Org. Chem.* **31**, 2397 (1966); M. Tomoeda, R. Kikuchi, M. Urata, and T. Futamura, *Chem. Pharm. Bull.* **18**, 542 (1970).

¹⁶⁴ A. J. Solo, H. S. Sachdev, and S. S. H. Gilani, *J. Org. Chem.* **30**, 769 (1965).

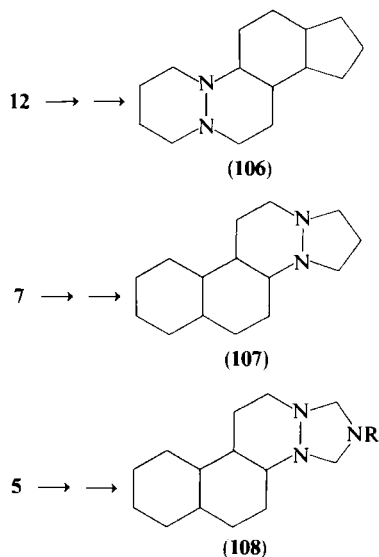
¹⁶⁵ J. Yoshizawa and M. Tomoeda, *J. Chem. Soc. C*, 1741 (1971); M. Kocor and F. Snatzke, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **23**, 113 (1975) [*CA* **83**, 114731 (1975)].

¹⁶⁶ M. Lora-Tamayo, *Comment.—Pontif. Acad. Sci.* **2**, (1971) [*CA* **84**, 17235 (1976)].

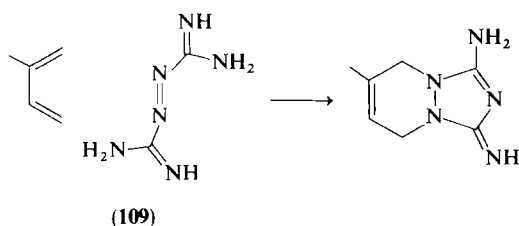
¹⁶⁷ S. F. Nelsen, W. C. Hollinsed, L. A. Grezzo, and W. P. Parmelee, *J. Am. Chem. Soc.* **101**, 7347 (1979).

¹⁶⁸ M. F. Brana and J. L. Soto, *An. Quim.* **70**, 970 (1974); B. Lopez, M. Lora-Tamayo, P. Navarro, and J. L. Soto, *Heterocycles* **2**, 649 (1974).

¹⁶⁹ J. E. Prickett and B. T. Gillis, *J. Heterocycl. Chem.* **13**, 1333 (1976); J. M. Castellano, M. F. Brana, M. Lora-Tamayo, and J. L. Soto, *Tetrahedron Lett.*, 4141 (1977).



The azodiamidine (**109**) also gives Diels–Alder adducts with simple dienes. The initial adducts readily undergo ring closure to give 1,2,4-triazolo-pyridazines.¹⁷⁰



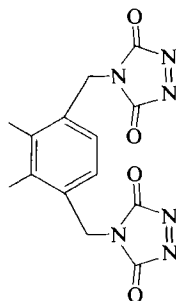
Bis-1,2,4-triazole-3,5-diones such as **110** have also been used in Diels–Alder reactions, and give bispyridazines.¹⁷¹ The pyridazine derivative **111** is formed in quantitative yield from PTAD and 2,7-dimethyl-2,3,5,6-octatetraene,¹⁷² and the azadiene, 4-aza-1,3,5-triphenylpenta-2,4-diene, also reacts readily with PTAD to give **112**.¹⁷³ There are many other examples of Diels–Alder additions of ADC compounds to simple acyclic dienes which proceed entirely as expected; the above selection has been limited to reactions of synthetic potential and with novel features.

¹⁷⁰ G. F. Wright, *Can. J. Chem.* **30**, 62 (1952); G. Pirisino and F. Sparatore, *Boll. Chim. Farm.* **113**, 421 (1974) [*CA* **82**, 112020 (1975)].

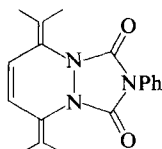
¹⁷¹ K. Wald and H. Wamhoff, *Chem. Ber.* **111**, 3519 (1978).

¹⁷² C. Boan and L. Skattebol, *J. C. S. Perkin I*, 1568 (1978).

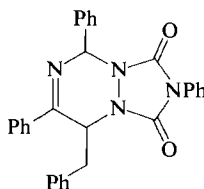
¹⁷³ D. H. Hunter and R. P. Steiner, *Can. J. Chem.* **53**, 355 (1975).



(110)

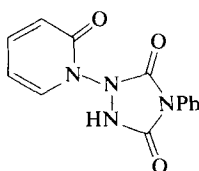


(111)

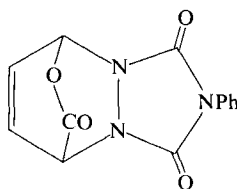


(112)

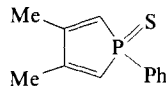
Cyclic dienes also react readily with ADC compounds although in many cases the initial adducts are not isolable. 1-Substituted pyrid-2-ones give Diels–Alder adducts with ADC compounds, although 2-pyridone itself gives only the substitution product (e.g., **113**).¹⁷⁴ 2-Pyrone gives a 1:2 adduct with PTAD, since the initial adduct (**114**) rapidly loses CO₂ to generate a diene which then reacts with more PTAD.¹⁷⁵ The initial adducts of ADC compounds with cyclopentadienones,¹⁷⁶ and 3,4-dimethyl-1-phenylphosphole 1-sulfide (**115**)¹⁷⁷ also regenerate a diene by loss of CO and PhP=S, respectively.



(113)



(114)



(115)

Furans add to DEAZD to give Diels–Alder adducts, although short reaction times are essential if the initial adduct is to be isolated. Attempts to convert the adduct into the bicyclic compound **116** failed. The only product isolated was a trimer of 4,5-dihydropyridazine, possibly formed as shown in Scheme 16.¹⁷⁸ However, the furan adducts are readily converted

¹⁷⁴ V. V. Kane, H. Werblood, and S. D. Levine, *J. Heterocycl. Chem.* **13**, 673 (1976); N. P. Shusherina and M. Said, *Dokl. Akad. Nauk SSSR* **233**, 606 (1977) [*CA* **87**, 39382 (1977)].

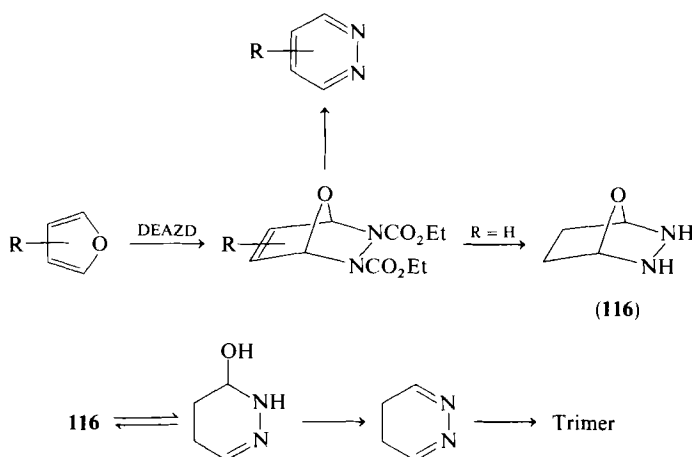
¹⁷⁵ N. P. Shusherina and M. Said, *J. Org. Chem. USSR (Engl. Transl.)* **12**, 2201 (1976).

¹⁷⁶ W. Ried and R. D. Reinhard, *Justus Liebigs Ann. Chem.* **729**, 69 (1969); W. Ried and S.-H. Lim, *Justus Liebigs Ann. Chem.*, 129 (1973).

¹⁷⁷ Y. Kashman and O. Awerbouch, *Tetrahedron* **31**, 53 (1975).

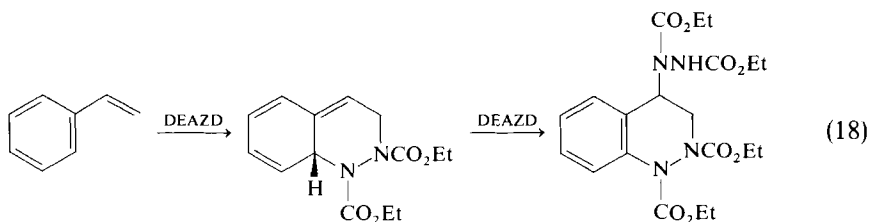
¹⁷⁸ B. K. Bandlish, J. N. Brown, J. W. Timberlake, and L. M. Trefonas, *J. Org. Chem.* **38**, 1102 (1973).

into aromatic pyridazines in moderate yields by treatment with acid followed by hydrazine.¹⁷⁹ 5-Ethoxyoxazoles give Diels–Alder adducts with ADC compounds,¹⁸⁰ but isoindoles do not.¹⁴⁴



SCHEME 16

Another important class of dienes which react readily with ADC compounds are the vinyl arenes. However, the reaction of styrene with ADC compounds does not give simple tetrahydrocinnolines. Styrene and DEAZD give a 1:2 adduct formed by the initial Diels–Alder adduct reacting rapidly in an ene reaction with more DEAZD (Eq. 18).¹⁸¹ Substituted styrenes react



similarly.¹⁸² The reaction of styrene with PTAD also gives 1:2 adducts, although the actual product depends on the conditions. The initial Diels–Alder adduct reacts with further PTAD by two competing pathways. At

¹⁷⁹ K. N. Zelenin and I. P. Bezhan, *Dokl. Akad. Nauk SSSR* **191**, 1292 (1970) [*CA* **73**, 35307 (1970)].

¹⁸⁰ N. Sh. Padyukova and V. L. Florent'ev, *Chem. Heterocycl. Compd. (Engl. Transl.)* **9**, 555 (1973).

¹⁸¹ O. Diels and K. Alder, *Justus Liebigs Ann. Chem.* **450**, 237 (1926); G. Ahlgren, B. Akermarck, J. Lewandowska, and R. Wahren, *Acta Chem. Scand., Ser. B* **B29**, 524 (1975).

¹⁸² K. Alder and H. Niklas, *Justus Liebigs Ann. Chem.* **585**, 97 (1954).

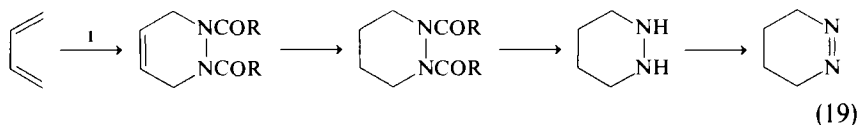
- ¹⁸³ K. B. Wagener, S. R. Turner, and G. B. Butler, *J. Polym. Sci., Part B* **10**, 805 (1972); C. Seoane and J. L. Soto, *An. Quim.* **73**, 1035 (1977).
- ¹⁸⁴ A. G. M. Willems, R. R. van Eck, H. Nijhuis, U. K. Pandit, and H. O. Huisman, *Recl. Trav. Chim. Pays-Bas* **89**, 885 (1970).
- ¹⁸⁵ H. Straub, *Chem.-Ztg.* **98**, 457 (1974).
- ¹⁸⁶ P. B. Terent'ev, A. N. Kost, and V. G. Kartsev, *Chem. Heterocycl. Compd. (Engl. Transl.)* **12**, 590 (1976); P. B. Terent'ev, V. G. Kartsev, and A. N. Kost, *ibid.* **808**; P. B. Terent'ev, N. G. Kotova, and A. N. Kost, *ibid.* **14**, 534 (1978); P. B. Terent'ev, V. G. Kartsev, I. K. Yakushenko, L. N. Prostakova, A. N. Kost, and I. P. Glorizov, *Khim. Geterotsikl. Soedin., Sb.* **15**, 639 (1979) [*CA* **91**, 91584 (1979)]; A. Kost, P. B. Terent'ev, V. G. Kartsev, and I. K. Yakushenko, *U.S.S.R. Patent* 517,590 (1976) [*CA* **85**, 123958 (1976)].
- ¹⁸⁷ G. Jones and P. Rafferty, *Tetrahedron Lett.*, 2731 (1978).
- ¹⁸⁸ W. A. Pryor, J. H. Coco, W. H. Daly, and K. N. Houk, *J. Am. Chem. Soc.* **96**, 5591 (1974).
- ¹⁸⁹ C. J. Moody, C. W. Rees, and S. C. Tsoi, unpublished results.
- ¹⁹⁰ J. M. Weinman, Ph.D. Thesis, University of Minnesota, 1964; R. J. Sundberg, "The Chemistry of Indoles," p. 127. Academic Press, New York, 1970.

TABLE I
CLEAVAGE/HYDROLYSIS OF ADC:DIENE ADDUCTS

$$\begin{array}{c} \diagup \text{NR} \\ \diagdown \text{NR} \end{array} \longrightarrow \begin{array}{c} \diagup \text{NH} \\ \diagdown \text{NH} \end{array}$$

| R | Method | Reference |
|--|--|-----------|
| CO ₂ CH ₃ | KOBu- <i>t</i> /DMSO/H ₂ O/25°C | 192 |
| | LiSMe/HMPT/25°C | 193 |
| CO ₂ CH ₂ CH ₃ | KOH/EtOH or HOCH ₂ CH ₂ OH/125°C | 194 |
| | Me ₃ SiI/CHCl ₃ /70°C | 195 |
| CO ₂ CH ₂ CCl ₃ | Zn/AcOH/THF/0°C | 196 |
| | Electrolysis | 197 |
| CO ₂ CH ₂ CH ₂ Ts | NaOEt/EtOH/25°C or below | 198 |
| CO ₂ CH ₂ Ph | H ₂ /Pd-C | 199 |
| CO ₂ CMe ₃ | Trifluoroacetic acid | 187 |
| PO(OPh) ₂ | 2 N aqueous HCl/100°C | 200 |

(19). Virtually all bicyclic azoalkanes are made via this route from cyclic 1,3-dienes. (For a recent review on azoalkanes, see Ref. 191.) Azodicarboxylic



esters are most commonly used as the ADC component, and since the hydrolysis step often requires quite vigorous conditions (strong base, high temperature) considerable variations and modifications have been introduced. These are summarized in Table I.^{187,192-200} Oxidation to the azo compound is often spontaneous in air, or is readily effected by many reagents, the most commonly used being copper(II) chloride. This permits isolation

¹⁹¹ P. S. Engel, *Chem. Rev.* **80**, 99 (1980).

¹⁹² E. A. Wildi and B. K. Carpenter, *Tetrahedron Lett.*, 2469 (1978); D. W. Whitman and B. K. Carpenter, *J. Am. Chem. Soc.* **102**, 4272 (1980).

¹⁹³ R. D. Little and M. G. Venegas, *J. Org. Chem.* **43**, 2921 (1978).

¹⁹⁴ P. G. Gassman, *Org. Synth.* **49**, 1 (1969).

¹⁹⁵ M. E. Jung and M. A. Lyster, *J. C. S. Chem. Commun.*, 315 (1978).

¹⁹⁶ W. H. Rastetter, *J. Am. Chem. Soc.* **98**, 6350 (1976).

¹⁹⁷ R. D. Little and G. L. Carroll, *J. Org. Chem.* **44**, 4720 (1979).

¹⁹⁸ S. Masamune, N. Nakamura, and J. Sapadaro, *J. Am. Chem. Soc.* **97**, 918 (1975).

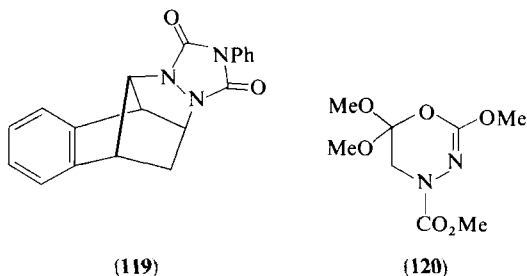
¹⁹⁹ M. L. Heyman and J. P. Snyder, *Tetrahedron Lett.*, 2859 (1973); R. Askani and M. Wieduwilt, *Chem. Ber.* **109**, 1887 (1976); R. N. Warrenner, R. A. Russell, and R. Y. S. Tan, *Tetrahedron Lett.*, 1589 (1978).

²⁰⁰ J. L. Miesel, *Tetrahedron Lett.*, 3847 (1974).

of the copper(I) complex of the azo compound.¹⁹⁴ PTAD is also widely used in the synthesis of bicyclic azoalkanes,²⁰¹ although again the conditions required to cleave the triazole ring are often fierce. This disadvantage can be overcome by using 1,3,4-thiadiazole-2,5-dione (11) in place of PTAD; the adducts being cleaved under much milder hydrolysis conditions.³⁷ Nevertheless, PTAD adducts are widely used as precursors for the azoalkane intermediates in the synthesis of strained hydrocarbons such as prismane and semibullvalane.^{202,203} Treatment of PTAD adducts with KOH in ethylene glycol, followed by hydrogen peroxide leads directly to cyclic azoxy compounds, although the method often works better on the MTAD adducts.²⁰⁴

3. Reaction with Monoenes

The reaction of acyclic ADC compounds with monoenes has already been discussed in Sections III,B and IV,B. In certain cases the major reaction pathway involves addition of the ADC compound as a 4π component, to the monoene to give 1,3,4-oxadiazines (Scheme 1). 1,3,4-Oxadiazines are the major or sole products from the reactions of ADC compounds with indene,⁸⁰ and 4-nitrophenyl vinyl ether,⁹⁰ and from the reaction of azodibenzoyl with enamines and enol ethers.⁹¹⁻⁹³ Norbornadiene also gives a 1,3,4-oxadiazine (42) with ADC compounds.⁸² However, benzonorbornadiene behaves differently, and the major product from the reaction with PTAD has the structure 119.²⁰⁵ Other bicyclic monoenes react similarly.²⁰⁶ 1,3,4-



²⁰¹ E. L. Allred and A. L. Johnson, *J. Am. Chem. Soc.* **93**, 1300 (1971); D. Kaufmann and A. De Meijere, *Tetrahedron Lett.*, 779 (1979); J. J. Tufariello, J. H. Chang, and A. C. Bayer, *J. Am. Chem. Soc.* **101**, 3315 (1979).

²⁰² T. J. Katz and N. Acton, *J. Am. Chem. Soc.* **95**, 2738 (1973).

²⁰³ L. A. Paquette, R. E. Wingard, and R. K. Russel, *J. Am. Chem. Soc.* **94**, 4739 (1972).

²⁰⁴ J. P. Snyder, V. T. Bandurco, F. Darack, and H. Olsen, *J. Am. Chem. Soc.* **96**, 5158 (1974); H. Olsen and J. P. Snyder, *ibid.* **99**, 1524 (1977); **100**, 285 (1978).

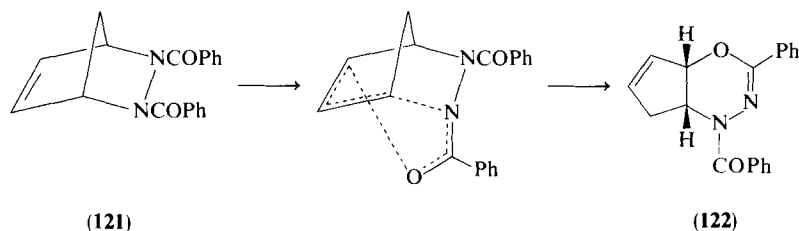
²⁰⁵ W. Adam, O. De Lucchi, and I. Erden, *Angew. Chem., Int. Ed. Engl.* **18**, 468 (1979).

²⁰⁶ W. Adam, O. De Lucchi, and I. Erden, *J. Am. Chem. Soc.* **102**, 4806 (1980).

Oxadiazines (**120**) are formed from ketene acetals and DMAZD in moderate yields.¹⁰⁶

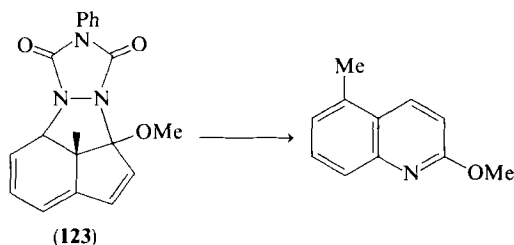
4. By Further Transformation of Initial Adducts

In certain cases the initial Diels–Alder adducts of ADC compounds are labile. For example, the adduct (**121**) from cyclopentadiene and azodibenzoyl rearranges in quantitative yield on heating in aqueous methanol to give the 1,3,4-oxadiazine **122**.²⁰⁷ Solvent has little or no effect, and a concerted [3,3] rearrangement as shown in Scheme 17 seems the most likely explanation. The rearrangement has been extensively studied by Mackay and co-workers,²⁰⁸ and it shows great dependence on substitution effects.



SCHEME 17

The PTAD adduct (**123**) from the 3a*H*-indene (**91**) rearranges and fragments on pyrolysis. The heterocyclic product is 2-methoxy-5-methylquinoline. This novel fragmentation reaction is under further investigation.²⁰⁹

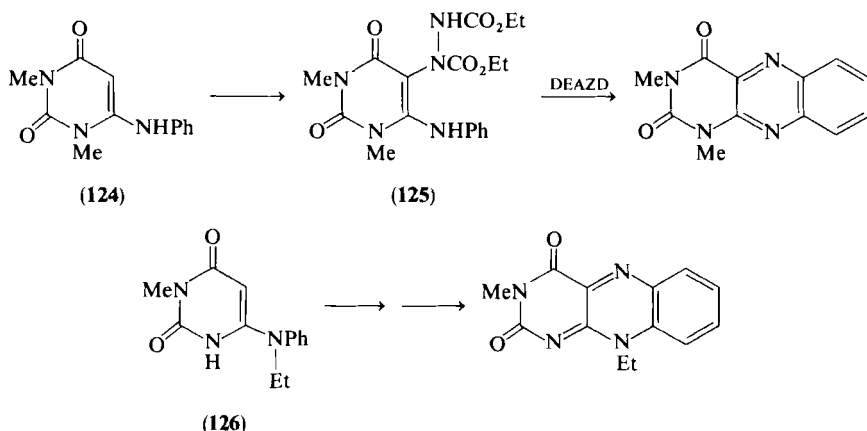


²⁰⁷ L. A. Carpino and E. S. Rundberg, *J. C. S. Chem. Commun.*, 1431 (1968); D. Mackay, J. A. Campbell, and C. P. R. Jennison, *Can. J. Chem.* **48**, 81 (1970).

²⁰⁸ J. A. Campbell, D. Mackay, and T. D. Sauer, *Can. J. Chem.* **50**, 371 (1972); C. Y. J. Chung, D. Mackay, and T. D. Sauer, *ibid.*, 3315; D. Mackay, C. W. Pilger, and L. L. Wong, *J. Org. Chem.* **38**, 2043 (1973); J. A. Campbell, I. Harris, D. Mackay, and T. D. Sauer, *Can. J. Chem.* **53**, 535 (1975); Le H. Dao and D. Mackay, *ibid.* **56**, 1724 (1978).

²⁰⁹ T. L. Gilchrist, C. W. Rees, and D. Tuddenham, unpublished result.

The purine synthesis described in Section IV,C,3, in which an ADC compound acted as a source of one nitrogen atom for the heterocycle, has been extended to the synthesis of six-membered ring alloxazines. Reaction of DEAZD with 6-anilino-1,3-dimethyluracil (**124**) at 180°C gives 1,3-dimethylalloxazine presumably via the initial adduct **125**. Again, excess DEAZD is required; **125** does not cyclize on heating alone.²¹⁰ Use of the *N*-ethyl derivative (**126**) gives isoalloxazines.²¹¹ The reaction has also been used for the synthesis of 7-azaxanthopterin.²¹²



E. PREPARATION OF LARGER RINGS

Very few examples of ADC compounds being used in the synthesis of larger ring heterocycles have been reported. PTAD adds to cyclooctatetraene in Diels–Alder fashion (a rare example of a 1,4-addition to cyclooctatetraene),²¹³ and to tropone to give large rings.²¹⁴ The tropone adduct (**127**) is transformed to the diazepine **128** by a series of photolysis and methanolysis reactions. 1-Substituted-3-oxidopyridiniums add to DEAZD to give seven-membered rings.²¹⁵ The adduct from 4,4-dimethylpyrazole-3,5-dione and 4,4-dimethyl-3,5-diphenyl-4*H*-pyrazole (as diene) gives

²¹⁰ F. Yoneda, S. Matsumoto, Y. Sakuma, and S. Fukazawa, *J. C. S. Perkin I*, 1907 (1975).

²¹¹ F. Yoneda, Y. Sakuma, T. Nagamatsu, and S. Mizumoto, *J. C. S. Perkin I*, 2398 (1976).

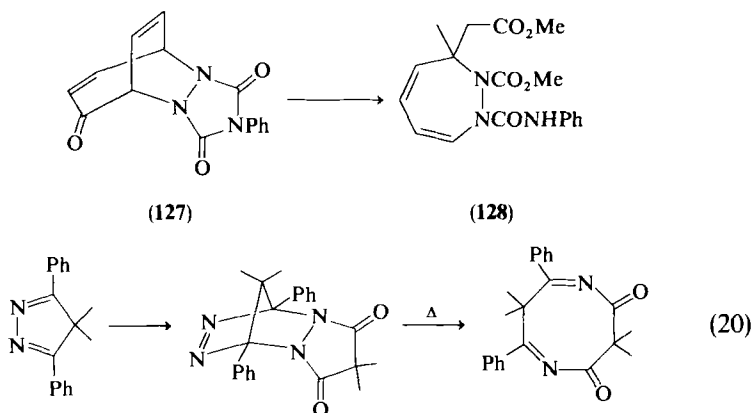
²¹² E. C. Taylor and A. J. Cocuzza, *J. Org. Chem.* **44**, 1125 (1979).

²¹³ A. B. Evnin, R. D. Miller, and G. R. Evanega, *Tetrahedron Lett.*, 5863 (1968).

²¹⁴ T. Sasaki, K. Kanematsu, and K. Hayakawa, *J. Chem. Soc. C*, 2142 (1971).

²¹⁵ N. Dennis, A. R. Katritzky, and S. K. Parton, *Chem. Pharm. Bull.* **23**, 2899 (1975); Y. Tamura, M. Akita, H. Kiyokawa, L. C. Chen, and H. Ishibashi, *Tetrahedron Lett.*, 1751 (1978).

2,4-diphenyl-3,3,7,7-tetramethyl-1,5-diazocine-6,8-dione on heating (Eq. 20.).³¹

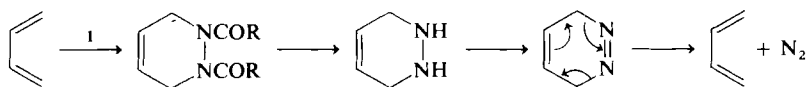


V. Other Reactions of Azodicarbonyl Compounds

Other major uses of ADC compounds which do not give heterocyclic products are summarized briefly in this section.

A. PROTECTION OF DIENES

In recent years ADC compounds have found wide use in the protection of 1,3-dienes. The Diels–Alder adducts, which because of the powerful dienophilic properties of ADC compounds are formed under mild conditions, can be reconverted to the diene by a series of hydrolysis, decarboxylation and oxidation reactions, followed by “spontaneous” loss of N_2 (Scheme 18). In the preparation of cyclic azoalkanes (Section IV,D,2) a hydrogenation step is usually included (Eq. 19). The sequence is exemplified in Paquette’s use of PTAD to protect the diene system of [4.4.2]propella-2,4,11-triene,²¹⁶ and in the protection of the diene system in levopimaric acid.²¹⁷ However, in the

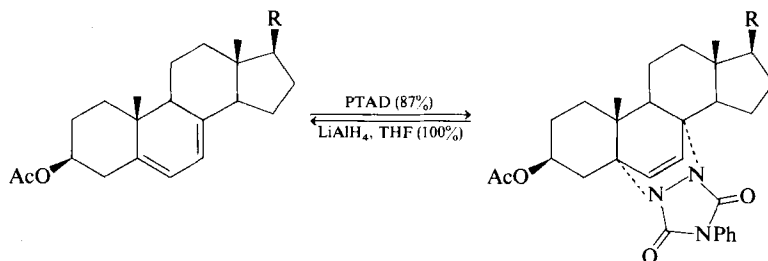


SCHEME 18

²¹⁶ L. A. Paquette, R. P. Micheli, and J. M. Photis, *J. Am. Chem. Soc.* **99**, 7911 (1977).

²¹⁷ G. Mehta, *Indian J. Chem.* **7**, 565 (1969).

critical protection of the steroid 5,7-diene system, this method of regenerating the diene gave poor results. A simple thermal retro Diels–Alder reaction also gave poor yields, as did heating the adduct in the presence of excess furan to intercept the ADC compound (PTAD in most cases) as it was re-formed. The best method of regenerating dienes from their PTAD adducts is probably treatment with LiAlH_4 in THF which, in the case of ergosteryl acetate, gives 100% conversion.²¹⁸ Hence PTAD is now widely used in



steroid chemistry,²¹⁹ although it was found unsuitable for the protection of the vitamin D_3 diene system.²²⁰ Pyridazine-3,6-dione²²¹ and phthalazine-1,4-dione²²² have also been used successfully in the steroid field, but DEAZD failed to give Diels–Alder adducts with steroid ring B dienes; only ene products were isolated.²²³ Steroid ring B diene:PTAD adducts have been used in other ways. Treatment of the cholesta-5,7-dien-3-ol adduct with boron trifluoride etherate leads to a loss of 4-phenylurazole accompanied by a rearrangement to the anthrasteroid **129**. The PTAD adduct of cholesta-5,7-dien-3-one gives the trienone **130** on similar treatment.²²⁴ Hence, an overall conversion of diene to a triene can be achieved via the diene–PTAD adduct.

²¹⁸ D. H. R. Barton, T. Shioiri, and D. A. Widdowson, *J. Chem. Soc. C*, 1968 (1971).

²¹⁹ C. Kaneko, A. Sugimoto, Y. Eguchi, S. Yamada, M. Ishikawa, S. Sasaki, and T. Suda, *Tetrahedron* **30**, 2701 (1974); D. H. R. Barton, A. A. L. Gunatilaka, T. Nakanishi, H. Patin, D. A. Widdowson, and B. R. Worth, *J. C. S. Perkin I*, 821 (1976); M. Tada and A. Oikawa, *J. C. S. Chem. Commun.*, 727 (1978).

²²⁰ D. J. Aberhardt and A. C.-T. Hsu, *J. Org. Chem.* **41**, 2098 (1976).

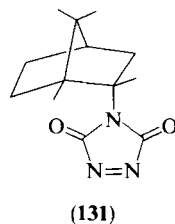
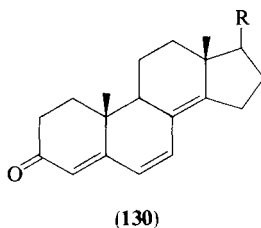
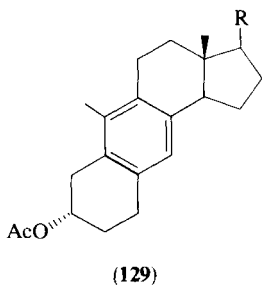
²²¹ P. E. Georgiou and G. Just, *J. C. S. Perkin I*, 888 (1973).

²²² N. A. Bogoslovskii, G. E. Litvinova, and G. I. Samokhvalov, *Zh. Obshch. Khim.* **48**, 908 (1978) [*CA* **89**, 163848 (1978)].

²²³ A. van der Gen, J. Lakeman, M. A. M. P. Gras, and H. O. Huisman, *Tetrahedron* **20**, 2521 (1964); J. Lakeman, W. N. Speckamp, and H. O. Huisman, *ibid.* **24**, 5151 (1968); H. de Nijs and W. N. Speckamp, *Tetrahedron Lett.*, 813 (1973).

²²⁴ N. Bosworth, A. Emke, J. M. Midgley, C. J. Moore, W. B. Whalley, G. Ferguson, and W. C. Marsh, *J. C. S. Perkin I*, 805 (1977); A. Emke, D. Hands, J. M. Midgley, W. B. Whalley, and R. Ahmed, *ibid.*, 820.

Finally, the chiral 1,2,4-triazole-3,5-dione (**131**) has been used to resolve "chiral" dienes such as 1,2,3-trimethylcyclooctatetraene.²²⁵



B. INTERCEPTION OF REACTIVE DIENES

Because of its great reactivity PTAD has found wide use in the interception of reactive, unstable dienes. For example, unstable isoindenes,²²⁶ 3aH-indenes,¹⁴⁶ 1,3-divinylallenes,²²⁷ and benzene oxides²²⁸ have all been successfully trapped with PTAD. 4-(4-Bromophenyl)-1,2,4-triazole-3,5-dione (**5**, R = 4-Br—C₆H₄) is often used if the derivatives are required for X-ray structure determination.²²⁹ Azodicarboxylic esters have been used to trap tetra(trifluoromethyl)cyclobutadiene,²³⁰ and spiro[4.4]nonatetraene.²³¹

At the other extreme of diene reactivity, some dienes are so unreactive that only powerful dienophiles such as PTAD will undergo Diels–Alder reactions with them. Thus, 4,5-dimethylene-1,3-dioxolan-2-one fails to react with TCNE or maleic anhydride, but gives the required Diels–Alder adduct (63%) with PTAD.²³² The powerful dienophilic properties of PTAD have

²²⁵ J. M. Gardik and L. A. Paquette, *Tetrahedron Lett.*, 3597 (1979); L. A. Paquette, R. F. Doehner, J. A. Jenkins, and J. F. Blount, *J. Am. Chem. Soc.* **102**, 1189 (1980).

²²⁶ K. Mackenzie, and W. P. Lay, *Tetrahedron Lett.*, 3241 (1970); K. K. de Fonseka, C. Manning, J. J. McCullough, and A. J. Yarwood, *J. Am. Chem. Soc.* **99**, 8257 (1977).

²²⁷ U. Mödlhammer and H. Hopf, *Angew. Chem., Int. Ed. Engl.* **14**, 501 (1975).

²²⁸ M. P. Servé and D. M. Jerina, *J. Org. Chem.* **43**, 2711 (1978).

²²⁹ V. M. Kobal, D. T. Gibson, R. E. Davis, and A. Garza, *J. Am. Chem. Soc.* **95**, 4420 (1973).

²³⁰ T. Kobayashi, I. Kumadaki, A. Oshawa, Y. Hanzawa, M. Honda, and Y. Iitaka, *Tetrahedron Lett.*, 3001 (1975).

²³¹ M. F. Semmelhack, J. S. Foos, and S. Katz, *J. Am. Chem. Soc.* **94**, 8637 (1972); **95**, 7325 (1973).

²³² H. D. Scharf and H. Plum, *Justus Liebigs Ann. Chem.*, 27 (1977); H. D. Scharf, H. Plum, J. Fleischhauer, and W. Schleker, *Chem. Ber.* **112**, 862 (1979).

also found use in natural product structure determination,²³³ and in the selective removal of 1,3-dienes from complex hydrocarbon mixtures.²³⁴

C. OTHER REACTIONS

In general, ADC compounds are good hydrogen acceptors and have found use as such in synthesis. DEAZD is widely used in conjunction with Ph_3P for reactions which formally involve a dehydration.²³⁵ Both DEAZD and PTAD oxidize alcohols to aldehydes and ketones,²³⁶⁻²³⁸ and are used as dehydrogenating agents, particularly in heterocyclic synthesis for the $-\text{NHNH}-$ to $-\text{N}=\text{N}-$ conversion.^{126,239,240} PTAD oxidizes 1,1-disubstituted hydrazines to aminonitrenes, and simultaneously acts as a trapping reagent for the "nucleophilic" nitrene to give stable aminoazirines.^{241,242} No cycloaddition of the nitrene to the $-\text{N}=\text{N}-$ was observed (cf. Section IV,A).

VI. Conclusion

This review has attempted to bring together the reactions of ADC compounds which are useful in heterocyclic synthesis, and to develop the general trends that have so far appeared in their reactivity. Thus, in general, ADC compounds are more powerful dienophiles than the corresponding $\text{C}=\text{C}$ compounds, particularly when the azo bond is in the cis configuration. However, they are also more reactive as enophiles and electrophiles, and may react as such even in cases where Diels-Alder (or other) cycloaddition is formally possible, and where the corresponding $\text{C}=\text{C}$ compounds do react as dienophiles. Nevertheless, despite this added complication, the major use of ADC compounds has been as dienophiles in the synthesis of pyridazines

²³³ H. H. Sun and W. Fenical, *Tetrahedron Lett.*, 685 (1979).

²³⁴ M. L. Poutsma and P. A. Ibarbia, *Tetrahedron Lett.*, 4967 (1970); M. F. Semmelhack and R. J. De Franco, *J. Am. Chem. Soc.* **94**, 8838 (1972).

²³⁵ For an example of use in macrocyclic lactone formation see B. Seuring and D. Seebach, *Justus Liebigs Ann. Chem.*, 2044 (1978), and references therein.

²³⁶ F. Yoneda, K. Suzuki, and Y. Nitta, *J. Am. Chem. Soc.* **88**, 2328 (1966).

²³⁷ R. C. Cookson, I. D. R. Stevens, and C. T. Watts, *J. C. S. Chem. Commun.*, 744 (1966).

²³⁸ Le H. Dao and D. Mackay, *Can. J. Chem.* **57**, 2727 (1979).

²³⁹ G. Seitz and H. Hoffmann, *Synthesis*, 201 (1977).

²⁴⁰ B. Fuchs, W. D. Kwalwasser, and M. Rosenblum, *Isr. J. Chem.* **13**, 107 (1975).

²⁴¹ R. Ahmed and J.-P. Anselme, *Can. J. Chem.* **50**, 1778 (1972).

²⁴² J. E. Weidenborner, E. Fahr, M. J. Richter, and K.-H. Koch, *Angew. Chem., Int. Ed. Engl.* **12**, 236 (1973).

and derivatives, cyclic azoalkanes, and in the protection and trapping of dienes. The reactivity of ADC compounds as 2π components extends to other cycloaddition reactions, for example with 1,3-dipoles to give a wide range five-membered ring heterocycles, and with monoenes to give four-membered rings, although this latter reaction is often complicated by the fact that acyclic ADC compounds can also act as 4π components.

It seems likely that ADC compounds will continue to find use as reactive dienophiles, this reaction being well established by now, and it will be interesting to see if any of their less well known reactions are further exploited in heterocyclic synthesis.

Addendum

Several relevant papers and review articles have appeared recently. These contain reports on the mechanism and kinetics of the ene reaction of ADC compounds,²⁴³⁻²⁴⁵ examples of four-membered ring formation,²⁴⁶⁻²⁴⁷ other cycloadditions of ADC compounds,²⁴⁸⁻²⁵² the synthesis of azoalkanes,²⁵³ the use of chiral 1,2,4-triazole-3,5-diones,²⁵⁴ and the use of the DEAZD/ Ph_3P reagent in organic synthesis.²⁵⁵

ACKNOWLEDGMENT

The author would like to thank Professor C. W. Rees for his advice and encouragement throughout this project.

²⁴³ C. A. Seymour and F. D. Greene, *J. Am. Chem. Soc.* **102**, 6384 (1980).

²⁴⁴ S. Ohashi, K. Leong, K. Matyjaszewski, and G. B. Butler, *J. Org. Chem.* **45**, 3467 (1980); S. Ohashi and G. B. Butler, *ibid.*, 3472; S. Ohashi, W. E. Ruch, and G. B. Butler, *ibid.* **46**, 614 (1981).

²⁴⁵ T. R. Hoyer, K. J. Bottorff, A. J. Caruso, and J. P. Dellaria, *J. Org. Chem.* **45**, 4287 (1980).

²⁴⁶ W. Adam and O. DeLucchi, *Tetrahedron Lett.* **22**, 929 (1981).

²⁴⁷ R. D. Wilcox, R. M. Pagni, H. M. Hassaneen, and G. W. Kabalka, *J. Org. Chem.* **46**, 1931 (1981).

²⁴⁸ S. Sommer and U. Schubert, *Angew. Chem., Int. Ed. Engl.* **18**, 696 (1979).

²⁴⁹ T. Wagner-Jauregg, *Synthesis*, 769 (1980).

²⁵⁰ M. Kuzuya, F. Miyake, and T. Okuda, *Tetrahedron Lett.* **21**, 2729 (1980).

²⁵¹ I. Erden and D. Kaufmann, *Tetrahedron Lett.* **22**, 215 (1981).

²⁵² Y. Kobayashi, T. Nakano, K. Shirahashi, A. Takeda, and I. Kumadaki, *Tetrahedron Lett.* **21**, 4615 (1980).

²⁵³ W. Adam and O. DeLucchi, *Angew. Chem., Int. Ed. Engl.* **19**, 762 (1980).

²⁵⁴ L. A. Paquette and R. F. Doehner, *J. Org. Chem.* **45**, 5105 (1980).

²⁵⁵ O. Mitsunobo, *Synthesis*, 1 (1981).

This Page Intentionally Left Blank

Sulfur Transfer Reagents in Heterocyclic Synthesis

MICHAEL DAVIS

*Department of Organic Chemistry, La Trobe University, Bundoora,
Victoria, Australia*

| | |
|---|----|
| I. Introduction | 48 |
| II. Hydrogen Sulfide, Sodium Sulfide, and Other Inorganic Salts | 49 |
| A. Hydrogen Sulfide | 49 |
| B. Sodium Sulfide | 51 |
| C. Thiocyanate Salts | 53 |
| III. Elemental Sulfur | 53 |
| A. General | 53 |
| B. Formation of Thiirenes | 54 |
| C. Formation of Thiophenes and Polycyclic Thiophenes | 54 |
| D. Formation of Isothiazoles and Benzisothiazoles | 54 |
| E. Formation of Other Heterocyclic Systems | 55 |
| IV. Sulfur Halides and Related Compounds of Divalent Sulfur | 55 |
| A. Sulfur Dichloride | 55 |
| B. Imide- <i>N</i> -sulfonyl Chlorides and <i>N,N'</i> -Thiobisimides | 57 |
| C. Disulfur Dichloride | 58 |
| D. <i>N,N'</i> -Dithiobisimides | 59 |
| E. Nitrile Sulfides | 59 |
| V. Tetravalent Sulfur Compounds | 60 |
| A. Sulfur Dioxide and Sulfite Esters | 60 |
| B. Thionyl Chloride | 62 |
| 1. Thiiranes | 62 |
| 2. Thietanones from Ketones | 62 |
| 3. Thiophenes | 63 |
| 4. Benzo[<i>b</i>]thiophenes and Thieno[3,2- <i>b</i>]thiophenes | 63 |
| 5. Isothiazoles | 64 |
| 6. 2,1-Benzisothiazoles | 64 |
| 7. Other Fused Isothiazoles | 65 |
| 8. Thiadiazoles | 65 |
| 9. Fused 1,2,5- and 1,2,3-Thiadiazoles | 66 |
| 10. Other Heterocyclic Systems | 66 |
| C. Sulfinylamines | 66 |
| D. Thiosulfinylamines | 68 |
| E. Sulfur Diimides | 68 |
| F. Thione <i>S</i> -Imides | 69 |
| G. Sulfines | 69 |
| H. Tetrasulfur Tetranitride and Related Sulfur-Nitrogen Compounds | 70 |

| | |
|---|----|
| VI. Hexavalent Sulfur Compounds | 71 |
| A. Sulfuryl Chloride | 71 |
| B. Sulfenes | 71 |
| C. Sulfonyl Imides | 72 |
| D. S,S-Diorganosulfodiimides. | 72 |
| VII. Thiocarbonyl Compounds | 73 |
| A. General | 73 |
| B. Thioketenes. | 73 |
| C. Thiophosgene | 74 |
| VIII. Phosphorus Sulfides | 75 |
| A. General | 75 |
| B. Phosphorus Pentasulfide | 75 |
| 1. Synthesis of Five-Membered Heterocycles. | 75 |
| 2. Synthesis of Six-Membered Heterocycles | 77 |
| C. "Phosphorus Trisulfide" | 78 |
| D. Triphenylphosphine Sulfide | 78 |

I. Introduction

Many sulfur-containing heterocyclic compounds can be constructed by reaction between an organic moiety and a simple, often inorganic, sulfur compound. This article is about such sulfur compounds and the typical heterocycle-forming reactions they undergo. In such reactions the sulfur atom, or a small group of contiguous atoms of which sulfur is one, is transferred to the organic substrate.

Some, perhaps most, of these cyclization reactions have no open-chain analog and are thus peculiar to heterocyclic synthesis; they can often provide simple and elegant (and inexpensive) preparations of certain heterocyclic compounds; some are used industrially for this reason.

The term "sulfur transfer reagent," first used by David Harpp,¹ implies a transfer of a sulfur-containing part of molecule X to molecule Y, with the remainder of molecule X being left behind or being eliminated in the course of the reaction. With this definition, elemental sulfur can hardly be described as a transfer reagent, but it is included nonetheless. Also included are a number of reactive intermediates, such as nitrile sulfides, formed from stable precursors.

A general review of this type has not previously been written, although more specialized articles, such as the review by Griffin, Woods, and Klayman² on the use of thioureas in the synthesis of heterocycles, are available. The literature of organic chemistry is so enormous that in order to keep this presentation reasonably short and concise heavy emphasis

¹ D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 1481 (1972).

² T. S. Griffin, T. S. Woods, and D. L. Klayman, *Adv. Heterocycl. Chem.* **18**, 99 (1975).

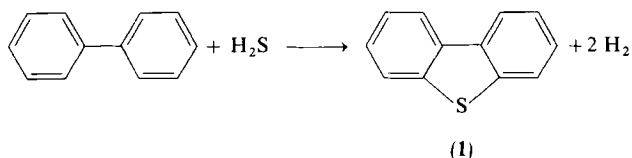
is given to work described in the last 10 years or so, up to about October 1980. Old established reactions are given only brief mention, usually by referring the reader to a readily available review. More detailed information on current work in the organic chemistry of sulfur can be obtained from the *Specialist Periodical Reports* of the Chemical Society (now the Royal Society of Chemistry).³ Only the most recent reports of a research group on a particular topic, rather than all the previous papers of a series, are included.

The classification adopted in this review is by type of sulfur reagent; it is useful to list by section the more important heterocycles that can be made: thiiranes, II,C, IV,B, VIII,D; thietanes and thietanones, V,B,2, VI,B, VII,B; thiazetidines, VI,B, VI,C, VII,B; thiophenes, II,A, III,C, V,B,3, VIII,B, VIII,C; benzothiophenes and polybenzothiophenes, II,A, II,B, IV,A, V,B,4; isothiazoles, III,D, V,A, V,B,5, V,F; benzisothiazoles, III,D, IV,E, V,B,6, V,C, V,E, VIII,B; 1,2,3-thiadiazoles, V,B,8, V,C, VII,C; 1,2,4-thiadiazoles, IV,A, IV,E; 1,3,4-thiadiazoles, V,C, VII,C; 1,2,5-thiadiazoles, IV,C, V,B,9, V,C, V,H.

II. Hydrogen Sulfide, Sodium Sulfide, and Other Inorganic Salts

A. HYDROGEN SULFIDE

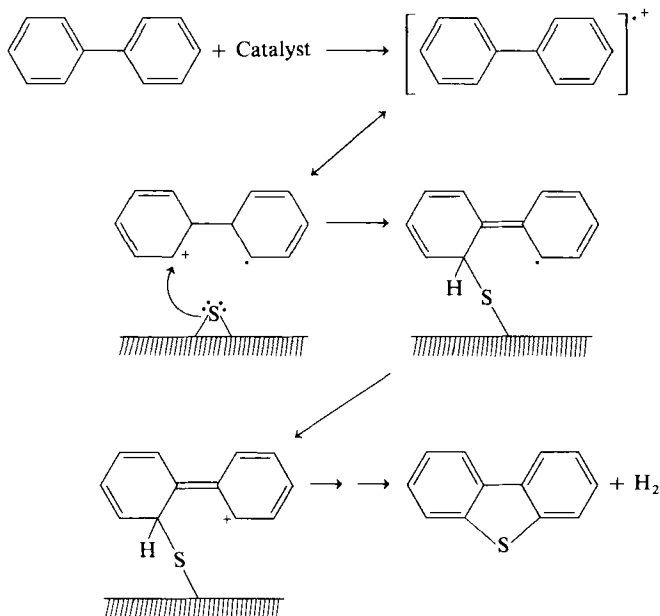
Klemm and co-workers have shown that polycyclic thiophenes are readily obtained by passing hydrogen sulfide and a hydrocarbon over a heterogeneous catalyst, usually a mixture of metallic oxides, at 450–630°C. A simple example of such a bridging sulfur insertion reaction is the production of the dibenzothiophene (1) from biphenyl.⁴ Compounds containing pyridine rings also undergo this bridging reaction. The thiophene ring is uncommon in present-day living systems, yet deposits of crude oil often contain substantial quantities of polycyclic thiophenes. Sulfur-bridging reactions of this sort may account for the occurrence of condensed thiophenes in geochemical samples, particularly as there is a correlation between the



³ D. H. Reid, "Organic Compounds of Sulphur, Selenium, and Tellurium," Reporter, Vol. 1. Chemical Society, London, 1970; Vol. 2, 1973; Vol. 3, 1975; Vol. 4, 1977; Vol. 5, 1979.

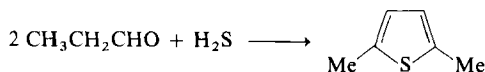
⁴ L. H. Klemm, J. J. Karchesy, and D. R. McCoy, *Phosphorus Sulfur* 7, 9 (1979).

quantity of these compounds and the sulfur content of the oil-bearing strata. The mechanism of the sulfur bridging may involve an ionic sulfur species, anchored to the catalyst surface, reacting with a hydrocarbon cation or cation-radical formed by one-electron transfer from the hydrocarbon to the catalyst (Scheme 1).⁴



SCHEME 1

Thiophenes can also be obtained from aldehydes, as in the synthesis of thiophene itself from crotonaldehyde (2-butenal), or the production of 2,4-dimethylthiophene from propanal; both reactions are carried out at high temperatures and in the presence of catalysts (Scheme 2).⁵

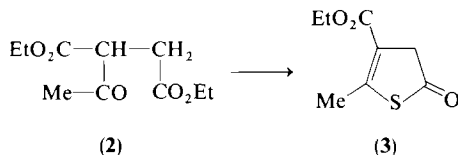


SCHEME 2

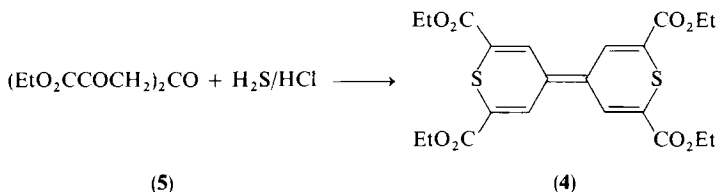
At lower temperatures oxygenated compounds may be isolated; thus the treatment of diethyl acetylsuccinate (**2**) with hydrogen sulfide yields the thiophene derivative (**3**).⁶

⁵ J. Barrault, M. Guisnet, J. Lucien, and R. Maurel, *J. Chem. Res., Synop.*, 207 (1978).

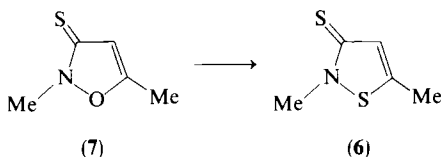
⁶ F. Duus, *J. C. S. Perkin I*, 292 (1978).



A more complex example of sulfur insertion is the formation of a bithiopyran (4) from an acyclic precursor (5) when treated with a mixture of hydrogen sulfide and hydrogen chloride.⁷

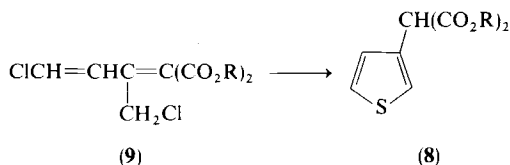


Sometimes, hydrogen sulfide converts an oxygen-containing heterocycle into a sulfur-containing one, and as furans and polycyclic furans are very common in nature such reactions may be the origin of the polycyclic thiophenes mentioned above. A typical example is the formation of the isothiazolin-3-thione (6) from the isoxazolin-3-thione (7) on treatment with hydrogen sulfide and hydrogen bromide.⁸



B. SODIUM SULFIDE

Reaction of a dihalide with sodium sulfide is perhaps the most direct way of creating a sulfur bridge; it has, for example, been used to synthesize the thiophene (8) from a dichloro-substituted precursor (9).⁹

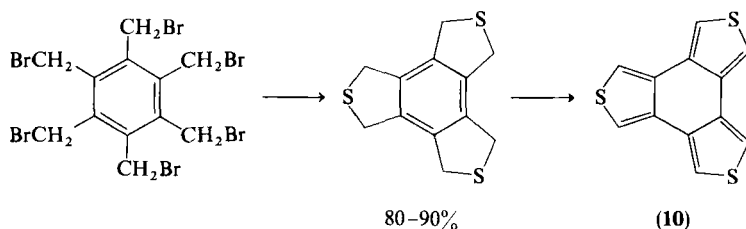


⁷ D. J. Sandman, T. J. Holmes, and D. E. Warner, *J. Org. Chem.* **44**, 880 (1979).

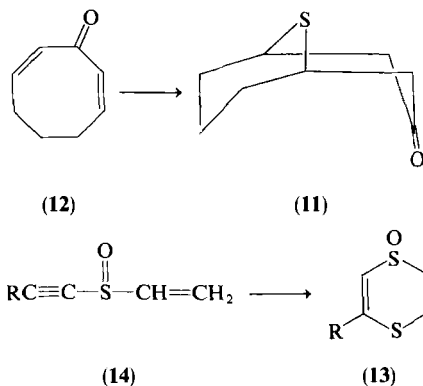
⁸ S. Sugai and K. Tomita, *Chem. Pharm. Bull.* **28**, 487 (1980).

⁹ J. P. Clayton, A. W. Guest, A. W. Taylor, and R. Ramage, *J. C. S. Chem. Commun.* 500 (1979).

There have been two other major applications of this type of reaction. In the first, in which five-membered rings are formed, an *o*-di(bromomethyl)-benzene affords a dihydrobenzo[*c*]thiophene which can be oxidized to a benzo[*c*]thiophene; a spectacular example of such a reaction is the formation of benzo[1,2-*c*:3,4-*c'*:5,6-*c''*]trithiophene (**10**) from hexakis-(bromomethyl)benzene.¹⁰ In the second, sulfur bridging is used to link together remote parts of a molecule, or separate molecules; the sulfur atom may subsequently be extruded, as in some syntheses of medium-sized rings or of cyclophanes. Unless high dilution techniques are used, other reactions such as the formation of linear or cyclic oligomers occur. Techniques making use of high-precision double-syringe reactors now circumvent such difficulties and allow the production of medium ring sulfides in reasonable yield.¹¹



Sodium sulfide or hydrosulfide can be used in double Michael additions; thus the bridged thiopyran (**11**) is formed from 2,7-cyclooctadienone (**12**),¹² and dihydrodithiin oxides (**13**) and related compounds are similarly produced from unsaturated sulfoxides (**14**).¹³



¹⁰ H. Hart and M. Sasaoka, *J. Am. Chem. Soc.* **100**, 4326 (1978).

¹¹ L. Mandolini and T. Vontor, *Synth. Commun.* **9**, 857 (1979).

¹² T. Sasaki, S. Eguchi, and T. Hioki, *J. Org. Chem.* **43**, 3808 (1978).

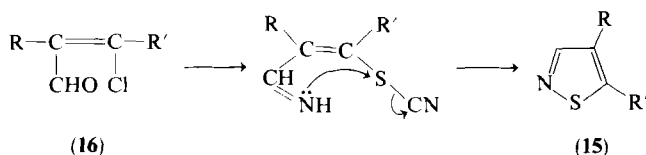
¹³ R. Verboom, M. Schoufs, J. Meijer, H. D. Verkruijsse, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **97**, 244 (1978); W. Verboom, R. S. Sukhai, and J. Meijer, *Synthesis*, 47 (1979).

C. THIOCYANATE SALTS

Thiocyanates have long been of importance in organosulfur chemistry; one particular use is the generation of the pseudohalogen thiocyanogen for the construction of, *inter alia*, thiazoles and benzothiazoles. Wood¹⁴ gave an early account of the reactions of thiocyanogen and this has been updated by Okafor¹⁵ and by Bonnett *et al.*¹⁶

A quite different use of a thiocyanate salt is the conversion of an epoxide (oxirane) to an episulfide (thiirane); this normally heterogeneous reaction is markedly accelerated by the use of silica gel coated with, or finely ground with, potassium thiocyanate, rather than with the thiocyanate salt alone.¹⁷

If ammonium thiocyanate is used, the ammonium ion can itself provide a nitrogen atom for heterocyclic ring construction. Such nitrogen and sulfur transfer is the basis of an elegant synthesis of isothiazoles (**15**) from 3-chloropropenals (**16**).¹⁸



III. Elemental Sulfur

A. GENERAL

The heating together of sulfur and an organic compound is the simplest possible heterocycle-forming reaction. This reviewer can recall, from his childhood reading of the *Boys' Own Paper* instructions for making large quantities of hydrogen sulfide from flowers of sulfur and mothballs (naphthalene), both readily available. Although simple to carry out, the mechanisms of these reactions are still in doubt. There are several general reviews on the reactions of sulfur, such as the one by Mayer¹⁹ but, surprisingly, not much on the formation of sulfur-containing heterocycles.

¹⁴ J. L. Wood, *Org. React.* **3**, 253 (1946).

¹⁵ C. O. Okafor, *Phosphorus Sulfur* **1**, 323 (1976).

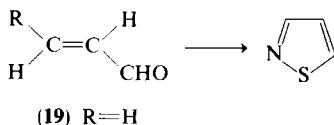
¹⁶ R. Bonnett, R. G. Guy, and D. Lanigan, *Phosphorus Sulfur* **2**, 95 (1976).

¹⁷ M. O. Brimeyer, A. Mehrota, S. Quici, A. Nigan, and S. L. Regen, *J. Org. Chem.* **45**, 4254 (1980).

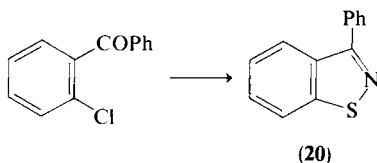
¹⁸ M. Muehlstaedt, R. Braemer, and B. Schulze, *J. Prakt. Chem.* **318**, 507 (1976).

¹⁹ R. Mayer, in "Organic Chemistry of Sulfur" (S. Oae, ed.), p. 33. Plenum, New York, 1977.

thiopropenals (**19**; R = thiocyanate, thiosulfate, etc.) with sulfur and ammonia.²³ In this case the ring sulfur atom comes from the elemental sulfur.



1,2-Benzisothiazoles (e.g., **20**) are available from a somewhat similar reaction between an *o*-chloroaryl ketone, sulfur, and ammonia.²⁴



E. FORMATION OF OTHER HETEROCYCLIC SYSTEMS

Many other nitrogen- and sulfur-containing rings are available from reactions of the Willgerodt–Kindler type. Benzo- and pyridino-fused thiazoles, for example, are formed from anilines (benzeneamines) and aminopyridines, respectively.²⁵ Asinger²⁶ has reviewed the scope of these reactions in heterocyclic synthesis.

IV. Sulfur Halides and Related Compounds of Divalent Sulfur

A. SULFUR DICHLORIDE

Alkenes and alkynes react with sulfur dichloride (SCl₂), giving 2-chloroethyl(or vinyl)sulfonyl chlorides. The reaction is an electrophilic addition to the multiple bond, and consequently the possible intermediacy of thiiranes, or thiiranium ions analogous to bromonium ions, has been

²³ F. Wille, W. Schwab, J. Schmitzer, and C. Jochum, *Chem. Ber.* **110**, 264 (1977).

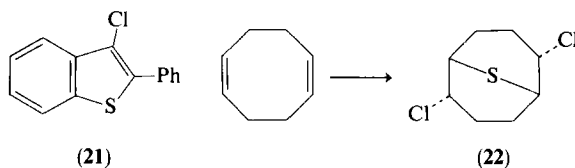
²⁴ J. Markert and H. Hagen, *Liebigs Ann. Chem.*, 768 (1980).

²⁵ T. Hisano and Y. Yabuta, *Chem. Pharm. Bull.* **21**, 511 (1973); F. Povazanec, B. Stanovnik, and M. Tisler, in "Organic Sulphur Chemistry" (C. J. M. Stirling, ed.), p. 420. Butterworth, London, 1975.

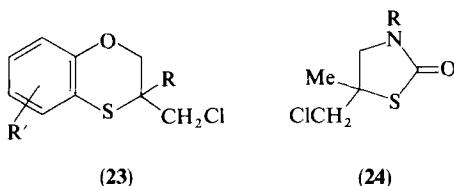
²⁶ F. Asinger, *Chem.-Ztg.* **98**, 610 (1974).

discussed but not proved.²⁷ With aryl alkenes or alkynes, or with dienes, further reactions can occur resulting in the formation of heterocycles; cyclic dienes yield sulfur-bridged systems.²⁸

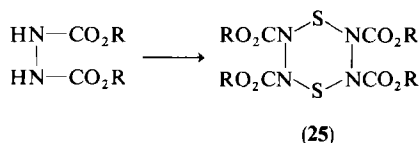
Typical examples are the formation of 3-chloro-2-phenylbenzo[*b*]-thiophene (**21**) in near quantitative yield from diphenylacetylene at room temperature,²⁷ and the synthesis of the dichlorothianonane (**22**) from 1,5-cyclooctadiene.²⁸



Muehlstaedt and co-workers have shown that similar sulfur bridges may be inserted into many other acyclic compounds; typical products include benzoxathiins (**23**) and thiazolinones (**24**).²⁹



In the examples above the sulfur dichloride links together two carbon atoms. It is equally possible to link two nitrogen atoms, as illustrated by the formation of a 1,4,2,3,5,6-dithiatetrazine (**25**) from a hydrazodicarboxylate ester.³⁰ Amidinium salts afford 1,2,3,5-dithiazolium salts (**26**).³¹



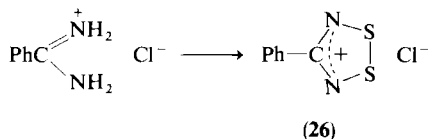
²⁷ T. J. Barton and R. G. Zika, *J. Org. Chem.* **35**, 1729 (1970); S. D. Ziman and B. M. Trost, *ibid.* **38**, 649 (1973).

²⁸ E. J. Corey and E. Block, *J. Org. Chem.* **31**, 1663 (1966).

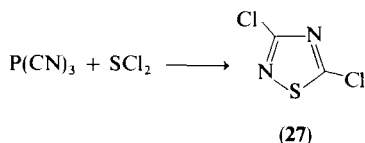
²⁹ M. Muehlstaedt, N. Stransky, A. Seifert, E. Kleinpeter, and H. Meinhold, *J. Prakt. Chem.* **320**, 113 (1978); M. Muehlstaedt and R. Widera, *ibid.*, 123.

³⁰ B. Weinstein, L. T. Hahn, and A. K. Eng, *J. Heterocycl. Chem.* **16**, 751 (1979).

³¹ G. G. Alange, A. J. Banister, B. Bell, and P. W. Millen, *J. C. S. Perkin I*, 1192 (1979).

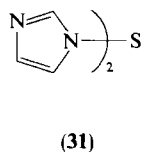
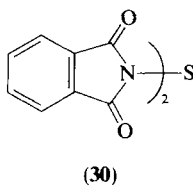
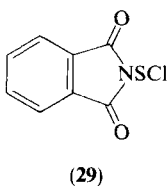
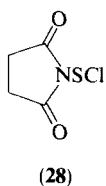


A nitrogen to carbon linkage is exemplified by the formation of dichloro-1,2,4-thiadiazole (27) from phosphorus tricyanide and sulfur dichloride.³²



B. IMIDE-*N*-SULFENYL CHLORIDES AND *N,N'*-THIOBISIMIDES

Sulfur dichloride is difficult to handle: it disproportionates readily, has an unpleasant odor, and tends to introduce extra, unwanted chlorine atoms. Several reagents have been developed, especially by Harpp and co-workers, in which these undesirable features have been modified or eliminated. Succinimide-*N*-sulfonyl chloride (28) and phthalimide-*N*-sulfonyl chloride (29) are both stable crystalline compounds which undergo many of the reactions of the sulfur dichloride itself. They can, for example, be used in a facile, high yield synthesis of thiiranes from alkenes.³³

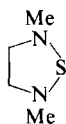


N,N'-Thiobisphthalimide (30) and 1,1'-thiobisimidazole (31) are two reagents of lesser reactivity; they are particularly effective in building sulfur bridges between nitrogen or oxygen atoms. The thiadiazoline (32), for example, is easily prepared from 30 and *N,N'*-dimethyl-1,2-diaminoethane.^{1,34}

³² A. E. Barnett, P. Piotis, and B. Tittle, *J. Inorg. Nucl. Chem.* **38**, 1575 (1976).

³³ M. V. Bombala and S. V. Ley, *J. C. S. Perkin I*, 3013 (1979).

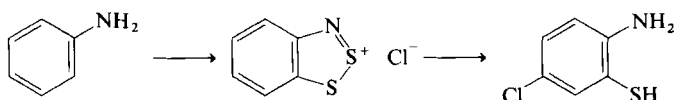
³⁴ D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 5313 (1972); *Int. J. Sulfur Chem.* **2**, 222 (1972); D. N. Harpp, K. Steliou, and T. H. Chan, *J. Am. Chem. Soc.* **100**, 1222 (1978).



(32)

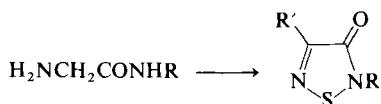
C. DISULFUR DICHLORIDE

The most important reaction of disulfur dichloride (S_2Cl_2) is with primary arylamines—the Herz reaction (Scheme 4). The Herz reaction has been reviewed and the mechanism of formation of the intermediates discussed.³⁵ Heteroaromatic primary amines react in similar fashion.³⁶



SCHEME 4

They have been several recent investigations of the reactions of disulfur dichloride with other organic substrates. Rokach and co-workers³⁷ have found that 2-aminoacetamides afford 2-substituted 1,2,5-thiadiazol-3(2*H*)-ones (33). This illustrates a frequent facet of such reactions: the elision of the second sulfur atom. A similar reaction, with loss of a sulfur atom, occurs with 2-alkylaminophenyl acetamides.³⁸

(33) $R' = H, Cl$

As mentioned earlier, attempts to make medium-size rings by sulfur-bridging reactions are fraught with difficulty, as linear polymers are often obtained. Reaction of *m*-dimethoxybenzene with disulfur dichloride in

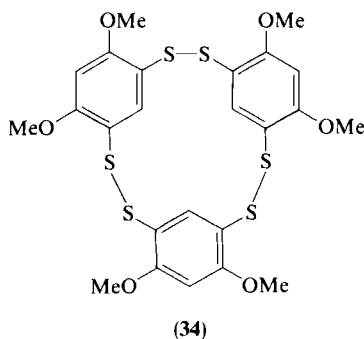
³⁵ W. K. Warburton, *Chem. Rev.* **57**, 1011 (1957); B. Kh. Strelets, L. S. Efros, and Z. V. Todres, *Chem. Heterocycl. Compd. (Engl. Transl.)* **6**, 327 (1970); S. Schneller, *Int. J. Sulfur Chem.* **8**, 485 (1973).

³⁶ P. I. Abramenko, T. K. Ponomareva, and G. I. Priklonskikh, *Chem. Heterocycl. Compd. (Engl. Transl.)* **15**, 387 (1979).

³⁷ J. Rokach, P. Hamel, Y. Girard, and G. Reader, *J. Org. Chem.* **44**, 1118 (1979).

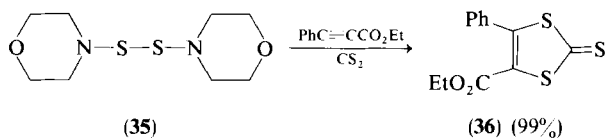
³⁸ K. Masuda, J. Adachi, and K. Nomura, *J. C. S. Chem. Commun.*, 331 (1979).

chloroform in the presence of iron powder afforded about 1.5% of the hexathia[2.2.2]metacyclophane (**34**).³⁹



D. *N,N'*-DITHIOBISIMIDES

Bismorpholino disulfide (**35**) and related compounds are prepared from the corresponding amine (or imide) and disulfur dichloride. An elegant synthesis of the 1,3-dithiole-2-thione (**36**) from **35** is shown; this is an example of two transfer reagents acting in concert.⁴⁰



E. NITRILE SULFIDES

Nitrile sulfides (**37**) have some, admittedly slight, structural affinity with the other nitrogen-sulfur reagents discussed in Section IV. They are unstable reactive intermediates that can be generated by the thermolysis of 1,3,4-oxathiazol-2-ones (**38**) or of 1,3,4-oxathiazoles (**39**).^{41,42} An alternative preparation is by the elimination of 2 moles of hydrogen fluoride from imini-sulfur difluorides (Scheme 5).⁴³ Nitrile sulfides (**37**) are capable of undergoing

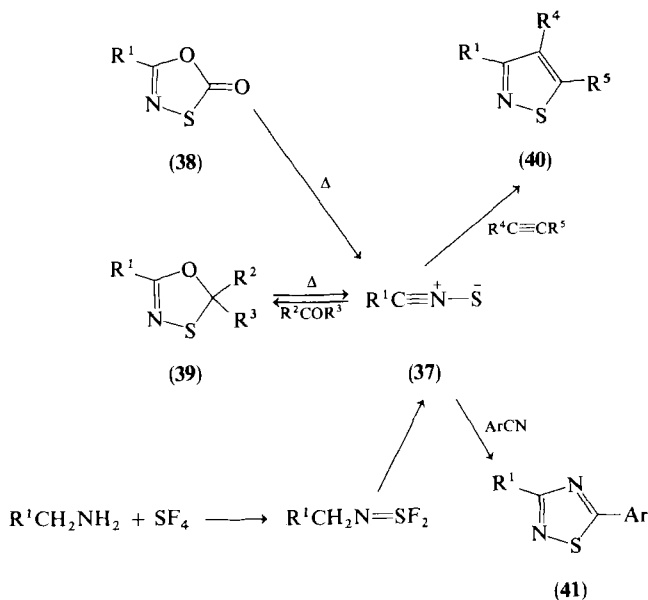
³⁹ F. Bottino, S. Foti, and S. Pappalardo, *J. C. S. Perkin I*, 1712 (1979).

⁴⁰ F. M. Benitez and J. R. Grunwell, *J. Org. Chem.* **45**, 2917 (1980).

⁴¹ R. K. Howe and J. E. Franz, *J. Org. Chem.* **39**, 962 (1974).

⁴² R. M. Paton, F. M. Robertson, J. F. Ross, and J. Crosby, *J. C. S. Chem. Commun.*, 714 (1980).

⁴³ M. J. Sanders, S. L. Dye, A. G. Miller, and J. R. Grunwell, *J. Org. Chem.* **44**, 510 (1979); M. J. Sanders and J. R. Grunwell, *ibid.* **45**, 3753 (1980).



SCHEME 5

1,3-dipolar additions with dipolarophiles. Alkynes yield isothiazoles (40) in a regiospecific reaction, and with nitriles 1,2,4-thiadiazoles (41) are produced.⁴³⁻⁴⁷ Nitrile sulfides also react with ketones, forming 1,3,4-oxathiazoles (39), or with activated alkenes, yielding isothiazolines.^{47,48} There are clearly many other reactions of nitrile sulfides still to be discovered.

V. Tetravalent Sulfur Compounds

A. SULFUR DIOXIDE AND SULFITE ESTERS

The reversible reaction between butadiene and sulfur dioxide, which yields sulfolene, has been known for a long time. Such cycloaddition reactions of sulfur dioxide, and of other sulfur oxides, have been reviewed by Block.⁴⁹

⁴⁴ J. E. Franz, R. K. Howe, and H. K. Pearl, *J. Org. Chem.* **41**, 620 (1976).

⁴⁵ R. K. Howe, T. A. Gruner, and J. E. Franz, *J. Org. Chem.* **42**, 1813 (1977).

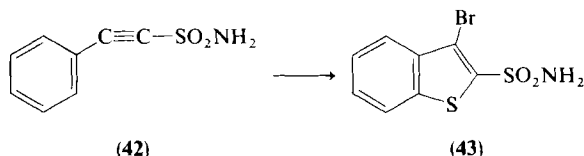
⁴⁶ R. K. Howe, T. A. Gruner, L. G. Carter, L. L. Black, and J. E. Franz, *J. Org. Chem.* **43**, 3736 (1978).

⁴⁷ R. K. Howe and J. E. Franz, *J. Org. Chem.* **43**, 3742 (1978).

⁴⁸ R. M. Paton, J. F. Ross, and J. Crosby, *J. C. S. Chem. Commun.*, 1146 (1979).

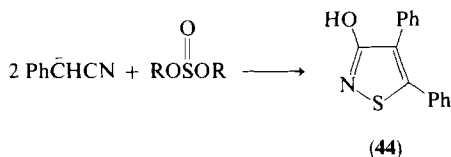
⁴⁹ E. Block, "Reactions of Organosulfur Compounds," p. 268. Academic Press, New York, 1978.

Smirnov-Zamkov *et al.* have shown that sulfur dioxide and hydrogen bromide react with alkynes; with phenylacetylene derivatives, such as the sulfonamide (42), a benzo[*b*]thiophene (43) is formed.⁵⁰ The mixture of sulfur dioxide and hydrogen bromide appears to behave like thionyl bromide, cf. thionyl chloride (see Section V,B).

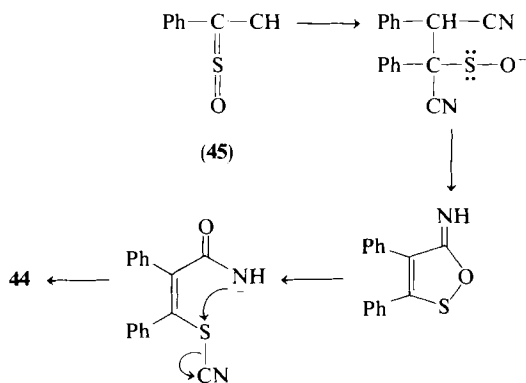


Sulfur dioxide has long been used in an industrial synthesis of isothiazole from propene, sulfur dioxide, and ammonia over a catalyst at 200°C.⁵¹

In a remarkable reaction, the anion of phenylacetonitrile was found to react with dialkyl sulfites to give 4,5-diphenylisothiazol-3-ol (44) in moderate



yield.⁵² A sulfine (45) formed from the sulfite and the anion was suggested as an initial intermediate.⁵² A proposal (Scheme 6) by J. A. Zoltewicz for the



SCHEME 6

⁵⁰ I. V. Smirnov-Zamkov, Yu. L. Zhorovskii, and V. I. Staninets, *Zh. Org. Khim.* **15**, 1782 (1979) [*CA* **92**, 41677 (1980)].

⁵¹ F. Hübenett, *Angew. Chem., Int. Ed. Engl.* **1**, 508 (1962); Hans J. Zimmer Verfahrenstechnik, U. S. Patent 2,257,409 (1966).

⁵² M. D. Scott, *J. C. S. Perkin I.* 1432 (1972).

subsequent mechanism looks more convincing but further work is clearly warranted on this unusual reaction.

B. THIONYL CHLORIDE

Thionyl chloride (SOCl_2) is the most versatile of all sulfur transfer reagents in heterocyclic synthesis. The sulfur-oxygen bond renders the sulfur atom more electrophilic; the possibility of ready removal by elimination of the oxygen atom allows easy aromatization of many of the initially formed sulfur heterocycles. Two general reviews of the chemistry of thionyl chloride are available.⁵³ Both cover the literature up to about 1970.

1. Thiiranes

Thiiranes (episulfides) have been suggested as intermediates in the reaction of thionyl chloride with various substrates including ketones and carboxylic acids.⁵⁴ However, apart from one claim, later corrected, no such compounds have been isolated.^{55,56}

2. Thietanones from Ketones

The reaction between thionyl chloride and ketones containing at least one α -hydrogen atom can give rise to many different products, the main heterocyclic compounds being 3-thietanones and benzo[*b*]thiophenes. Thietanones (e.g., **46**) are generally produced if the ketone has both α - and α' -protons. There has been debate about the initial attack of thionyl chloride on, particularly, methyl ketones containing an α' -methylene function. Pizey, who has reviewed the thionyl chloride-ketone reaction,⁵⁶ believes that the reactivity of α -protons is tertiary > secondary > primary. However, Sehgal and Krubsack^{56,57} have shown that in certain cases at least, preferential attack occurs at a methyl group rather than at a methinyl group.^{56,57} The product of such attack is a sulfinyl chloride (RSOCl), the sulfinyl group of

⁵³ M. Davis, H. Szkuta, and A. J. Krubsack, *Mech. React. Sulfur Compd.* **5**, 1 (1970); J. S. Pizey, "Synthetic Reagents," Vol. 1, p. 321. Ellis Horwood, Chichester, England, 1974.

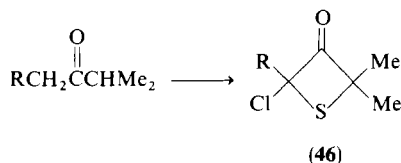
⁵⁴ A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 125 (1973).

⁵⁵ C. J. Ireland and J. S. Pizey, *J. C. S. Chem Commun.*, 4 (1972).

⁵⁶ J. S. Pizey and K. Symeonides, *Phosphorus Sulfur* **8**, 1 (1980).

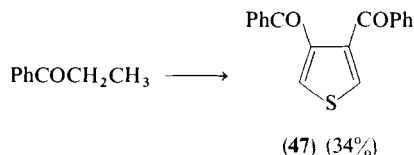
⁵⁷ A. J. Krubsack, R. Sehgal, W.-A. Loong, and W. E. Slack, *J. Org. Chem.* **40**, 3179 (1975); R. K. Sehgal and A. J. Krubsack, *Synth. Commun.* **10**, 245 (1980).

which may be reduced to sulfenyl by excess thionyl chloride before, or after, cyclization.



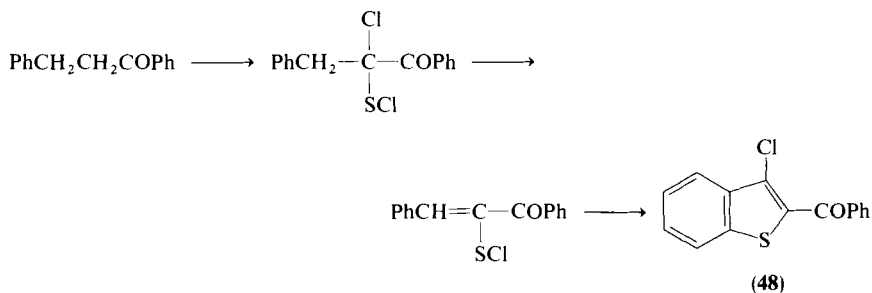
3. Thiophenes

A recent report indicates that thiophenes (not benzothiophenes) may be formed from alkyl phenyl ketones by treatment with a slight excess of thionyl chloride in the cold.⁵⁸ Propiophenone, for example, yields 3,4-dibenzoylthiophene (47). Adipic acid and related carboxylic acids yield thiophene derivatives upon treatment with thionyl chloride in the presence of pyridine.⁵⁹



4. Benzo[*b*]thiophenes and Thieno[3,2-*b*]thiophenes

In the reaction of ketones with thionyl chloride the intermediate sulfinyl (or sulfenyl) chloride can cyclize on to an aromatic ring located two carbon atoms away giving benzo[*b*]thiophenes (48) (Scheme 7).⁵⁴ Additional



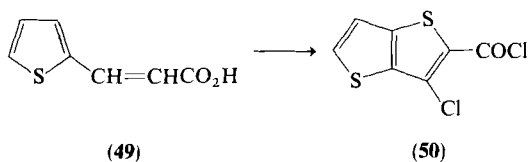
SCHEME 7

⁵⁸ K. Oka, *Heterocycles* **12**, 461 (1979).

⁵⁹ S. Nagakawa, J. Okumura, F. Sakai, H. Hoshi, and T. Naito, *Tetrahedron Lett.*, 3719 (1970).

chlorination in the heterocyclic ring (and occasionally in the benzenoid ring too) is a feature of these reactions. As might be expected from the likely reaction pathway, other substrates can be used, especially 3-phenylpropanoic, -propenoic, and -propynoic acids (hydrocinnamic, cinnamic, and phenylpropionic acids, respectively) and their esters can be used; all give benzo[*b*]-thiophenes. The reaction is greatly facilitated by an activated, electron-rich aromatic ring; mono-, di, and trimethoxyphenyl-substituted compounds give particularly good results.^{54,59,60}

3-(2-Thienyl)propenoic acid (**49**) reacts in a similar fashion with thionyl chloride at 100°C; the product, in low yield, is 3-chloro[3,2-*b*]thiophene-2-carbonyl chloride (**50**).⁶¹

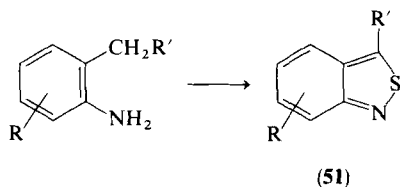


5. Isothiazoles

Isothiazoles can be prepared from thionyl chloride and α -aminoketones, α -iminoketones, α -iminonitriles, or acrylonitriles; the reactions concerned have been discussed.⁶²

6. 2,1-Benzisothiazoles

2,1-Benzisothiazoles (**51**) are available from the reaction of thionyl chloride with *o*-alkylbenzeneamines (*o*-toluidines).⁶³ Chlorinated by-products are



⁶⁰ W. B. Wright and H. J. Brabander, *J. Heterocycl. Chem.* **8**, 711 (1971); A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 4823 (1972); C. M. Bonnin, P. A. Cadby, C. G. Freeman, and A. D. Ward, *Aust. J. Chem.* **32**, 833 (1979).

⁶¹ W. B. Wright, *J. Heterocycl. Chem.* **9**, 879 (1972).

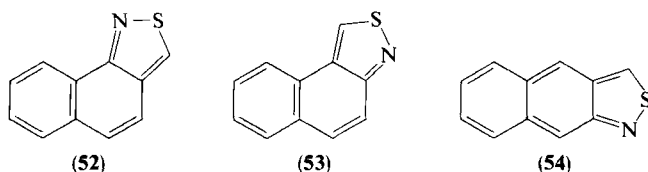
⁶² K. R. H. Wooldridge, *Adv. Heterocycl. Chem.* **14**, 7, 12 (1972).

⁶³ M. Davis and A. W. White, *J. C. S. Chem. Commun.*, 1547 (1968); *J. Org. Chem.* **34**, 2985 (1969); M. Davis, T. G. Paproth, and L. J. Stephens, *J. C. S. Perkin I*, 2057 (1973).

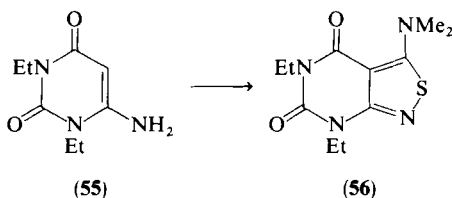
also produced. Chlorination occurs in the benzene ring para to the nitrogen atom, and at or in the side chain (R') of the heterocyclic ring. The Singerman reagent (Section V,C) avoids these chlorination problems. The mechanism of the cyclization has been discussed.⁶⁴

7. Other Fused Isothiazoles

Naphtho[1,2-*c*]isothiazole (**52**) and its [2,1-*c*] isomer (**53**) can be prepared from the corresponding methylnaphthaleneamines by a reaction similar to that described above; the linear isomer (**54**) is not obtainable in this way.⁶⁵

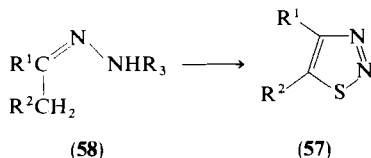


Reaction of the aminouracil (**55**) with thionyl chloride in dimethylformamide produced the isothiazolo[3,4-*d*]pyrimidine (**56**).⁶⁶



8. Thiadiazoles

1,2,3-Thiadiazoles (**57**) are produced by the reaction of *N*-substituted hydrazones (**58**; R^1 , R^2 = alkyl, aryl, H; R^3 = acetyl, ester, tosylate, etc.) with thionyl chloride.⁶⁷



⁶⁴ M. Davis, *Adv. Heterocycl. Chem.* **14**, 43 (1972).

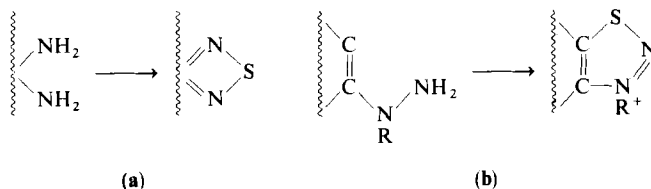
⁶⁵ M. Davis, G. C. Ramsay, and L. J. Stephens, *Aust. J. Chem.* **25**, 1355 (1972).

⁶⁶ Y. Furukawa, O. Miyashita, and S. Shima, *Chem. Pharm. Bull.* **24**, 970 (1976).

⁶⁷ H. Meier, G. Tricketts, E. Laping, and U. Merkle, *Chem. Ber.* **113**, 183 (1980).

9. Fused 1,2,5- and 1,2,3-Thiadiazoles

Very many fused 1,2,5-thiadiazoles, and some fused 1,2,3-thiadiazoles, have been prepared; the two typical reactions are illustrated (Scheme 8). The first is exemplified by the synthesis of numerous benzo- and hetero-fused 1,2,5-thiadiazoles by Carmack and co-workers,⁶⁸ and by Hartman's group;⁶⁹ an example of the second is the preparation of 1,2,3-thiadiazolo[4,5-*d*]-pyrimidines.⁷⁰



SCHEME 8

10. Other Heterocyclic Systems

Other heterocyclic systems prepared by a thionyl chloride reaction include fused thiazoles,⁷¹ thiatriazoles,⁷² oxathiins,⁷³ and dithiins;⁷⁴ some further examples are given in reviews.⁵³

C. SULFINYLAMINES

The chemistry and reactions of *N*-sulfinyl compounds have been summarized in two reviews appearing in the late 1960s and early 1970s.⁷⁵ There is also a short article in a recent comprehensive text.⁷⁶

⁶⁸ A. P. Komin and M. Carmack, *J. Heterocycl. Chem.* **12**, 829 (1975); **13**, 13 (1976).

⁶⁹ G. D. Hartman, S. E. Biffar, L. M. Weinstock, and R. Tull, *J. Org. Chem.* **43**, 960 (1978).

⁷⁰ K. Senga, M. Ichiba, and S. Nishigaki, *J. Org. Chem.* **43**, 1677 (1980).

⁷¹ I. M. Goldman, *J. Org. Chem.* **34**, 3285 (1969); H. D. O. Showalter, M. T. Shipchandler, L. A. Mitscher, and E. W. Hagaman, *ibid.* **44**, 3994 (1979).

⁷² S. D. Ziman, *J. Heterocycl. Chem.* **16**, 895 (1979).

⁷³ I. Granoth, *J. C. S. Perkin I*, 2166 (1974).

⁷⁴ A. Michailidis, M. Giraud, and D. Molho, in "Organic Sulphur Chemistry" (C. J. M. Stirling, ed.), p. 466. Butterworth, London, 1975.

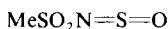
⁷⁵ G. Kresze, in "Organosulfur Chemistry" (M. J. Janssen, ed.), p. 259. Wiley (Interscience), New York, 1975; H. W. Roesky, in "Sulfur in Organic and Inorganic Chemistry" (A. Senning, ed.), Vol. 1, Chapter 9. Dekker, New York, 1971.

⁷⁶ C. R. Johnson, in "Comprehensive Organic Chemistry" (D. H. R. Barton and W. D. Ollis, eds.), Vol. 3, p. 241. Pergamon, Oxford, 1979.

Usually, *N*-sulfinyl compounds (**59**) behave as thionyl transfer reagents, similar to, but milder than, thionyl chloride. For example, *o*-diamines with *N*-sulfinylbenzeneamine (**59**; *R* = *Ph*) afford fused 1,2,5-thiadiazoles, as in Scheme 8a.⁷⁷ The advantage of using *N*-sulfinyl compounds, rather than thionyl chloride itself, is that concomitant chlorinations and oxidations are avoided. This is of particular importance in the synthesis of 2,1-benzisothiazoles (Section V,B,6). Singerman's reagent, *N*-sulfinylmethanesulfonamide (**60**) is especially valuable;⁷⁸ it was used very successfully in the synthesis of a series of benzobis(isothiazoles).⁷⁹

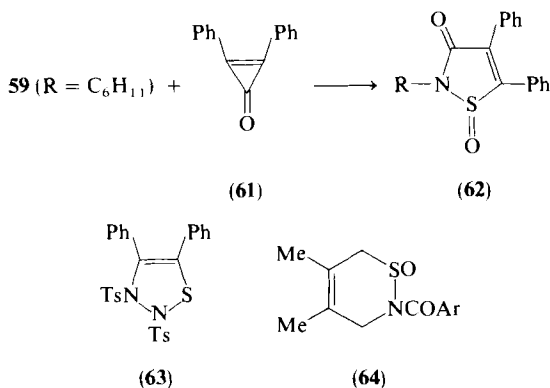


(59)



(60)

There have been some reports of the use of *N*-sulfinyl compounds to transfer both a nitrogen and a sulfur atom. An example is the reaction of *N*-sulfinylcyclohexylamine (**59**; *R* = cyclohexyl) with diphenylcyclopropenone in the presence of nickel tetracarbonyl. An isothiazolinone *S*-oxide (**62**) was the product.⁸⁰ Similarly, *N*-sulfinyl-*p*-toluenesulfonamide (**59**; *R* = tosyl) and the Wittig reagent triphenylphosphonium phenylbenzoylmethylide give 1,2,3-thiadiazoline (**63**).⁸¹



Soviet workers have studied reactions between *N*-sulfinylamines and 1,3-dienes; 1,2-thiazine derivatives (e.g., **64**) were formed.^{82,83} An earlier

⁷⁷ T. Uno, K. Takagi, and M. Tomoeda, *Chem. Pharm. Bull.* **28**, 1909 (1980).

⁷⁸ G. M. Singerman, *J. Heterocycl. Chem.* **12**, 877 (1975).

⁷⁹ B. Danylec and M. Davis, *J. Heterocycl. Chem.* **17**, 533, 537 (1980).

⁸⁰ A. Baba, Y. Ohshiro, and T. Agawa, *Chem. Lett.*, 11 (1976); Y. Ohshiro, H. Nanimoto, A. Baba, M. Komatsu, and T. Agawa, *Phosphorus Sulfur* **6**, 227 (1979).

⁸¹ T. Saito and S. Motoki, *J. Org. Chem.* **42**, 3922 (1977).

⁸² E. G. Kataev and V. V. Plemenkov, *Zh. Org. Khim.* **4**, 1094 (1968).

⁸³ E. M. Dorokhova, E. Levchenko, and N. P. Pel'kis, *Zh. Org. Khim.* **11**, 762 (1975).

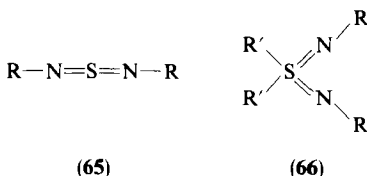
report of the formation of cycloaddition products from aldehydes and *N*-sulfinylamines has, however, now been shown to be incorrect.⁸⁴

D. THIOSULFINYLAMINES

Compounds containing the *N*-thiosulfinylamino group ($R-N=S=S$) have been reported recently.⁸⁵⁻⁸⁸ The aryl compounds are rather unstable purple oils which show promise as sulfur transfer agents, although few definitive examples have yet been reported.⁸⁷

E. SULFUR DIIMIDES

This is the name give by *Chemical Abstracts* to compounds with tetra-valent sulfur (**65**), but the nomenclature is confusing as the term "sulfodiiimide" is also applied to the hexavalent compounds (**66**). The former compounds (**65**) have been reviewed by Kresze,⁸⁸ and are briefly discussed below; the latter compounds (**66**) have been discussed by Haake⁸⁹ and are dealt with in Section VI,D.



The chemistry of the sulfur diimides (**65**) has been investigated in some detail, because such compounds might act as $S-N$ or $N-S-N$ transfer agents and thus allow access to novel heterocyclic systems. They are generally prepared by the action of sulfur tetrafluoride on primary amines.⁹⁰ Some of their reactions parallel those of the *N*-sulfinylamines— for example, the

⁸⁴ J. Mirek and S. Rachwal, *Phosphorus Sulfur* **3**, 333 (1977).

⁸⁵ D. H. R. Barton and M. J. Robson, *J. C. S. Perkin I*, 1245 (1974).

⁸⁶ S. Morimura, H. Horiuchi, C. Tamura, and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **53**, 1666 (1980).

⁸⁷ Y. Inagaki, R. Okazaki, and N. Inamoto, *Tetrahedron Lett.*, 293 (1977); Y. Inagaki, T. Hosogai, R. Okazaki, and N. Inamoto, *Bull. Chem. Soc. Jpn.* **53**, 205 (1980).

⁸⁸ G. Kresze, in "Organic Sulphur Chemistry" (C. J. M. Stirling, ed.), p. 65. Butterworth, London, 1975.

⁸⁹ M. Haake, *Top. Sulfur Chem.* **1**, 185 (1976).

⁹⁰ R. Appel, J. R. Lundein, and E. Lassmann, *Chem. Ber.* **109**, 2442 (1976); R. Appel and J. R. Lundein, *ibid.* **110**, 3205 (1977).

reaction of the trimethylsilyl derivative (**65**; $R = \text{SiMe}_3$) with certain compounds derived from 2-methylbenzeneamine yields 2,1-benzisothiazoles.⁹¹

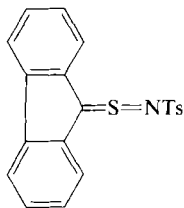
It is possible to incorporate the entire N—S—N moiety into a ring; the reaction of the *tert*-butyl derivative (**65**; $R = \text{CMe}_3$) with oxalyl chloride affords the thiadiazolidinedione (**67**).⁹²



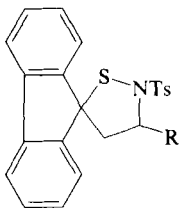
(67)

F. THIONE S-IMIDES

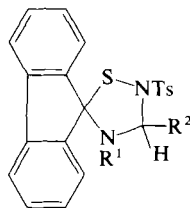
Thione *S*-imides, such as the fluorenethione *S*-tosylimide (**68**), have been known for about ten years. Saito and co-workers⁹³ have studied the cycloaddition reactions of **68** with compounds containing homonuclear and heteronuclear double bonds. In almost every case the imide (**68**) reacted as a 1,3-dipole; with alkenes, for example, isothiazoline derivatives (such as **69**) were formed and with azines the 1,2,4-thiadiazolidine derivatives (**70**) were produced.⁹³



(68)



(69)



(70)

G. SULFINES

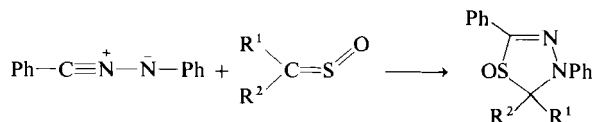
Sulfines ($\text{RR}'\text{C}=\text{S}=\text{O}$) are another type of thiocumulene and recently it has been demonstrated that they can participate in 1,3-dipolar cycloaddition

⁹¹ U. Klingebiel and D. Bentmann, *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **34B**, 123 (1979); see also M. Davis, *ibid.* **35B**, 405 (1980).

⁹² R. Neidlein and P. Leinberger, *Synthesis*, 63 (1977); *Chem.-Ztg.* **101**, 35 (1977).

⁹³ T. Saito and S. Motoki, *J. Org. Chem.* **44**, 2493 (1979); T. Saito, I. Oikawa, and S. Motoki, *Bull. Chem. Soc. Jpn.* **53**, 1023 (1980).

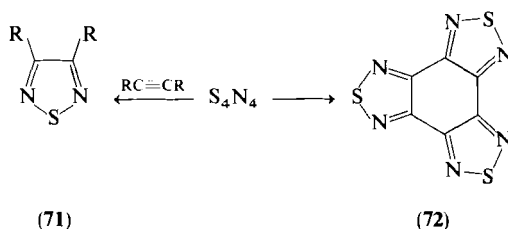
reactions. With diphenylnitrilimine, for example, the product is a 1,3,4-thiadiazole derivative (Scheme 9).⁹⁴



SCHEME 9

H. TETRASULFUR TETRANITRIDE AND RELATED SULFUR-NITROGEN COMPOUNDS

Tetrasulfur tetranitride has come under intensive scrutiny in recent years on account of its metallic nature, high electrical conductivity, and fascinating chemical properties—including its explosiveness in some circumstances. In reactions with organic substrates it can function as an N—S—N transfer agent; thus with acetylenes it affords 1,2,5-thiadiazoles (71),⁹⁵ and with *p*-dimethoxybenzene the trithiadiazole (72) is formed, although in rather low yield.⁹⁶ There is still much to discover about the chemistry of tetrasulfur tetranitride and of the many other cyclic sulfur-nitrogen compounds.⁹⁷ Preliminary results suggest that even longer concatenations of nitrogen and sulfur atoms may be transferable to organic substrates by some of these compounds.⁹⁸



Thiazyl fluoride (73) can be prepared from the corresponding chloride by halogen exchange; the chloride itself is obtained by the thermal depoly-

⁹⁴ B. F. Bonini, G. Maccagnani, G. Mazzanti, L. Thijs, G. E. Veenstra, and B. Zwanenburg, *J. C. S. Perkin I*, 1218 (1978).

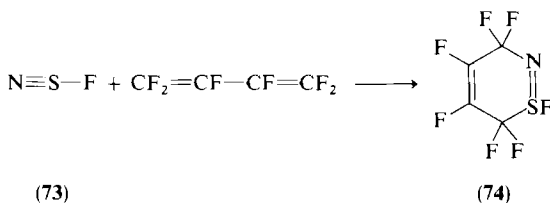
⁹⁵ M. Tashiro, S. Mataka, and K. Takahashi, *Heterocycles* **6**, 933 (1977); S. Mataka, K. Takahashi, Y. Yamada, and M. Tashiro, *J. Heterocycl. Chem.* **16**, 1009 (1979).

⁹⁶ S. Mataka, K. Takahashi, and M. Tashiro, *J. Heterocycl. Chem.* **14**, 963 (1977).

⁹⁷ A. J. Banister, *Phosphorus Sulfur* **5**, 147 (1978).

⁹⁸ H. W. Roesky, T. Müller, and E. Rodek, *J. C. S. Chem. Commun.*, 439 (1979); A. J. Banister, personal communication, 1980.

merization of its cyclic trimer. The reaction of thiazyl fluoride (73) with perfluoro-2-butyne affords a thiadiazole (71; $R = CF_3$) but with perfluoro-1,3-butadiene the N—S moiety is transferred intact and perfluoro-1,4,2-thiaza-1,4-cyclohexadiene (74) is produced. This is the first example of a $[4 + 2]$ addition to a formal $S \equiv N$ triple bond.⁹⁹



VI. Hexavalent Sulfur Compounds

A. SULFURYL CHLORIDE

The $S(VI)-O$ bond is not easily reduced, unlike the corresponding $S(IV)-O$ bond, and for this reason the chemistry of sulfonyl chloride (SO_2Cl_2), and of sulfonyl compounds generally, is not as rich or interesting as that of the sulfinyl compounds. Sulfonyl chloride is essentially a chlorine transfer agent. Reviews pertaining to the preparation of cyclic sulfate esters¹⁰⁰ and amides (cyclic sulfamides)¹⁰¹ using sulfonyl chloride are available.

B. SULFENES

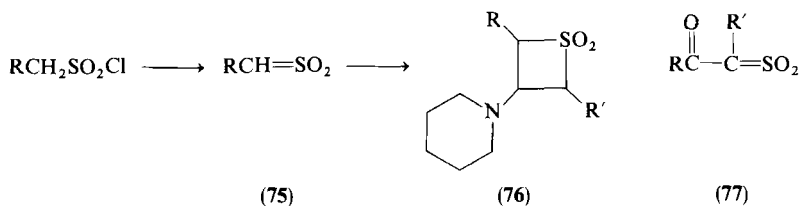
Alkylidene sulfenes (75), generally prepared by the dehydrohalogenation of alkylsulfonyl chlorides, add readily to electron-rich multiple bonds. For example, with enamines, the thietane dioxide (e.g., 76) is formed; diazoalkanes yield thiirane dioxides (episulfones); and imines (Schiff bases) afford 1,2-thiazetidine 1,1-dioxides. There are available numerous reviews of sulfenes, including cycloaddition reactions.¹⁰²

⁹⁹ W. Bludssus and R. Mews, *J. C. S. Chem. Commun.*, 35 (1979).

¹⁰⁰ E. T. Kaiser, in "Organic Chemistry of Sulfur" (S. Oae, ed.), p. 663. Plenum, New York, 1977.

¹⁰¹ G. A. Benson and W. J. Spillane, *Chem. Rev.* **80**, 151 (1980).

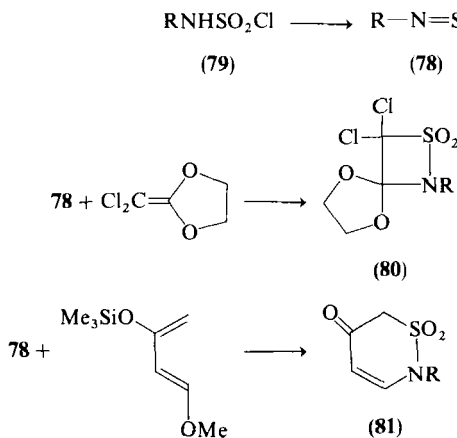
¹⁰² N. H. Fischer, *Synthesis* **2**, 393 (1970); T. Nagai and N. Tokura, *Int. J. Sulfur Chem., Part B* **7**, 207 (1972); J. F. King, *Acc. Chem. Res.* **8**, 10 (1975).



α -Ketosulfenes (77) have recently received attention as one type of carbonyl-conjugated thiocumulene; their role in heterocyclic synthesis has been recently discussed.¹⁰³

C. SULFONYL IMIDES

Sulfonyl imides (78) are, like sulfenes, prepared by dehydrohalogenation of the corresponding sulfonyl chlorides (79) (usually called sulfamoyl chlorides). Like sulfenes, they take part in [2 + 2] and [4 + 2] cycloaddition reactions with electron-rich alkenes or with 1,3-dienes, yielding 1,2-thiazetidine 1,1-dioxides (80)¹⁰⁴ or dihydro-1,2-thiazines (81),¹⁰⁵ respectively.



D. *S,S*-DIORGANOSULFODIIMIDES

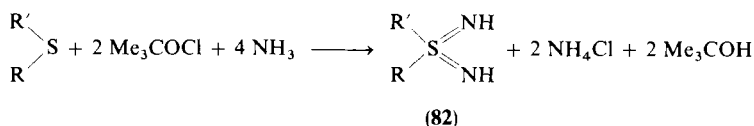
These interesting compounds (82) are usually prepared by oxidation of sulfides with chloramine generated *in situ* from ammonia and *tert*-butyl

¹⁰³ O. Tsuge, *Heterocycles* **12**, 1067 (1979).

¹⁰⁴ T. Nagai, T. Shingaki, M. Inagaki, and T. Ohshima, *Bull. Chem. Soc. Jpn.* **52**, 1102 (1979).

¹⁰⁵ J. A. Klock and K. L. Leschinsky, *J. Org. Chem.* **44**, 305 (1979); **45**, 721 (1980).

hypochlorite.¹⁰⁶ The nitrogen atoms are nucleophilic while the hydrogen atoms are capable of being replaced by another functionality. The chemistry of these compounds is, therefore, much more complex than that of the isoelectronic sulfones. Clearly, the two nitrogen atoms provide anchoring points for construction of novel heterocyclic rings. Haake and his co-workers, in particular, have prepared many fascinating compounds in which the —N=S(RR')=N— moiety is incorporated into a ring. He has written a comprehensive review.⁸⁹



VII. Thiocarbonyl Compounds

A. GENERAL

There is an enormous literature on thiocarbonyl compounds, due in part to the technical and industrial importance of many of them, including thioamides, thioureas, xanthates, dithiocarbamates and so forth. An excellent, and recent, general review is available.¹⁰⁷ There are also specialized reviews germane to the present chapter: Griffin, Woods, and Klayman² discussed the use of thioureas in the synthesis of heterocycles; the preparation of thiazoles from thioamides is included in a three-part volume on "Thiazoles"¹⁰⁸; the use of carbon disulfide in the synthesis of trithiones and related heterocycles has been reviewed by Mayer¹⁰⁹; and Huisgen¹¹⁰ has reported numerous examples of 1,3-dipolar cycloadditions in which carbon disulfide was used.

B. THIOKETENES

Thioketenes (**83**) are generally unstable and very reactive, although bis(trifluoromethyl)thioketene (**83**; $\text{R}^1 = \text{CF}_3$) is stable enough for isolation.

¹⁰⁶ M. Haake, *Tetrahedron Lett.*, 4449 (1970).

¹⁰⁷ F. Duus, in "Comprehensive Organic Chemistry" (D. H. R. Barton and W. D. Ollis, eds.), Vol. 3, p. 373. Pergamon, Oxford, 1979.

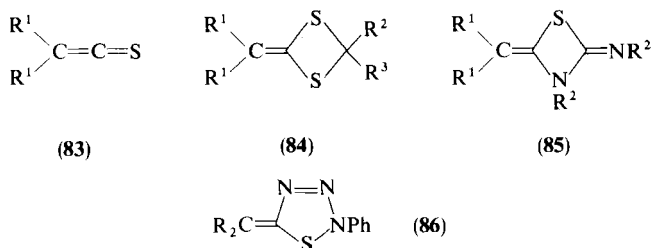
¹⁰⁸ A. Weissburger and E. C. Taylor, eds., "The Chemistry of Heterocyclic Compounds," Vol. 34 (in three parts). Wiley (Interscience), New York, 1979.

¹⁰⁹ R. Mayer, in "Organosulfur Chemistry" (M. J. Janssen, ed.), p. 219. Wiley (Interscience), New York, 1967.

¹¹⁰ See, for example, R. Huisgen and T. Schmidt, *Justus Liebigs Ann. Chem.*, 29 (1978).

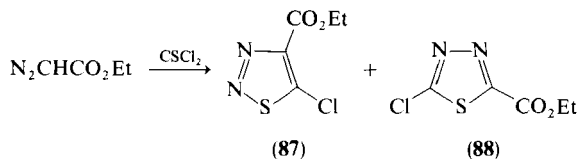
They can be prepared by the thermolysis of 1,2,3-thiadiazoles or by reaction of ketenes with phosphorus pentasulfide.¹¹¹⁻¹¹³

Raasch, and Schaumann and co-workers, have studied the reactions of bis(trifluoromethyl)thioketene (**83**; $R^1 = CF_3$) with alkenes, with thioketones, and with carbodiimides or Schiff-base imines. The products were, respectively, thietans, 1,3-dithietans (**84**; $R^1 = CF_3$), and 1,3-thiazetidines (**85**; $R^1 = CF_3$) (from the carbodiimide).^{114,115} With phenyl azide the 1,2,3,4-thiatriazoline (**86**; $R = CF_3$) is formed; subsequent pyrolysis yields 2,1-benzisothiazole.¹¹⁴



C. THIOPHOSGENE

Although thiophosgene ($CSCl_2$) was used by Woodward in his classic synthesis of isothiazoles from 3-aminopropenoate esters,¹¹⁶ it has not been used a great deal in the construction of sulfur-containing rings. In most cases the carbon atom, rather than the sulfur, is the ring-forming element. However, with α -diazocarbonyl compounds such as ethyl diazoacetate, both the carbon and sulfur atoms form part of the 1,2,3- and 1,3,4-thiadiazole rings (as in **87** and **88**) produced by the reaction with thiophosgene.¹¹⁷



¹¹¹ G. Seybold and C. Heibl, *Angew. Chem., Int. Ed. Engl.* **14**, 248 (1975); *Chem. Ber.* **110**, 1225 (1977).

¹¹² E. U. Elam, F. H. Rash, J. T. Dougherty, V. W. Goodlett, and K. C. Brannock, *J. Org. Chem.* **33**, 2738 (1968).

¹¹³ E. Schaumann and W. Walter, *Chem. Ber.* **107**, 3562 (1974).

¹¹⁴ M. S. Raasch, *J. Org. Chem.* **43**, 2500 (1978).

¹¹⁵ E. Schaumann, J. Ehlers, F.-F. Grabley, and S. Grabley, *Phosphorus Sulfur* **6**, 269 (1979).

¹¹⁶ K. R. H. Wooldridge, *Adv. Heterocycl. Chem.* **14**, 14 (1972).

¹¹⁷ P. Demaree, M. C. Doria, and J. M. Muchowski, *Can. J. Chem.* **55**, 243 (1977).

VIII. Phosphorus Sulfides

A. GENERAL

Although phosphorus trisulfide (P_4S_6 —but see below) and phosphorus pentasulfide (P_4S_{10}) have been widely used in the preparation of heterocyclic compounds there is no recent review. Weintraub has given an account of solvent- and temperature-dependent reactions of the pentasulfide, the compound employed in almost all recently reported work.¹¹⁸

B. PHOSPHORUS PENTASULFIDE

1. *Synthesis of Five-Membered Heterocycles*

Phosphorus pentasulfide is used to replace oxygen atoms with sulfur atoms; the reaction is commonly carried out in a solvent heated under reflux. Solvents employed include carbon disulfide, aromatic hydrocarbons, and pyridine. If an oxygen atom is part of a heterocycle, then the reagent *may* replace it with sulfur, as in the formation of 2,1-benzisothiazoles from 2,1-benzisoxazoles.¹¹⁹ Such replacements are, however, not general; some prior ring opening appears to be necessary before the reagent can act. For example, under normal conditions furan is not attacked.

A more common usage of phosphorus pentasulfide is to effect replacement of oxygen atoms in an acyclic compound. The thiated intermediate—which may be a fairly complex derivative containing phosphorus, sulfur, and oxygen atoms—then cyclizes with elimination. Except in one case, mentioned below, the intermediates seem not to have been studied in any detail.

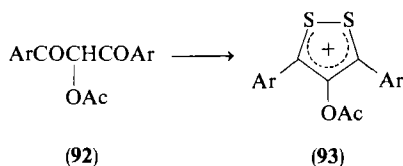
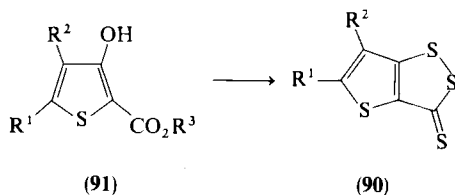
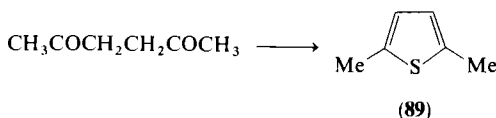
Examples of reactions involving replacement and cyclization are the long-known preparation of thiophenes (**89**) from 1,4-diketones, and the formation of 1,2-dithiole-3-thione (**90**) from the salicylate ester analog (**91**).¹²⁰ In the latter instance, oxidative cyclization with formation of an S—S bond has occurred; this is a common feature of these reactions, particularly if such a link is needed to complete a five-membered ring. Another example of this aspect is afforded by the reaction of the propane-1,3-dione derivatives (**92**) which yield 3,5-diaryl-1,2-dithiolylum salts (**93**) when heated with phosphorus pentasulfide in carbon disulfide, followed by perchloric acid.¹²¹

¹¹⁸ P. M. Weintraub, *Int. J. Sulfur Chem.* **8**, 321 (1973).

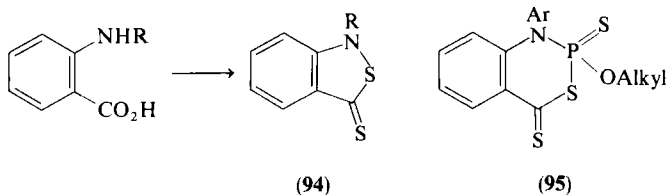
¹¹⁹ D. M. McKinnon and J. Y. Wong, *Can. J. Chem.* **49**, 2018 (1971); O. Aki, Y. Nakagawa, and K. Sirakawa, *Chem. Pharm. Bull.* **20**, 2372 (1972).

¹²⁰ J. Brelivet, P. Appriou, and J. Teste, *Bull. Soc. Chim. Fr.*, 1344 (1971).

¹²¹ D. Barillier, *Phosphorus Sulfur* **5**, 251 (1978).



The reagent does not replace nitrogen atoms, and N-alkyl or N-aryl anthranilic acids yield 2,1-benzisothiazoline-3-thiones (**94**) on heating with phosphorus pentasulfide in xylene. Curiously, when alkyl N-arylanthranilates are treated in the same way, only a very small proportion—less than 10%—of **94** is obtained. The major product (80%) is the cyclic phosphorus-containing compound (**95**), the identification of which gives some clue about the structures of possible intermediates.¹²²

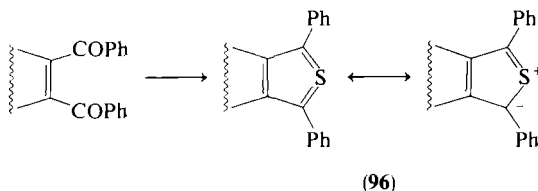


Potts and co-workers have used phosphorus pentasulfide and pyridine as a standard reagent for constructing annelated diphenylthiophene rings from *o*-dibenzoyl compounds. Many of these annelated thiophenes can be written only in the tetravalent sulfur or ylid dipolar form (**96**) and are thus termed “nonclassical”¹²³; other examples, particularly of the synthesis of nonclassical thienoisothiazoles, have been reported by Gotthardt.¹²⁴

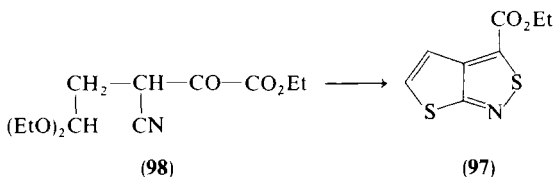
¹²² N. Lozac'h, *Int. J. Sulfur Chem., Part B* **6**, 131 (1971).

¹²³ K. T. Potts and S. Yao, *J. Org. Chem.* **44**, 977 (1979); K. T. Potts, H. P. Youzwak, and S. J. Zurawel, *ibid.* **45**, 90 (1980).

¹²⁴ H. Gotthardt and F. Reiter, *Tetrahedron Lett.*, 2163 (1976); H. Gotthardt, F. Reiter, R. Gleiter, and R. Bartetzko, *Chem. Ber.* **112**, 260 (1979).

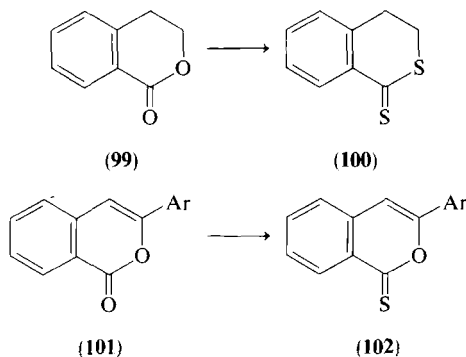


Double cyclizations can occur; one interesting example is the formation of the thieno[2,3-*c*]isothiazole (97) from the cyano-substituted ketoester (98).¹²⁵



2. Synthesis of Six-Membered Heterocycles

As with five-membered heterocycles, phosphorus pentasulfide may replace a ring oxygen atom by sulfur, or it may effect replacement in an acyclic precursor and then bring about cyclization. Thus isochroman-1-one (99) is converted into thioisochroman-1-thione (100); under the same conditions a 3-arylisocoumarin (101) produces a 3-aryl-1-thioisocoumarin (102) only, with no replacement of the ring oxygen atom.¹²² A typical example of thiation, followed by cyclization, is the formation of 2-alkyl- or 2-aryl-3,1-benzothiazine-4-thiones (103) from *N*-acylanthranilic acid esters (104) by treatment with phosphorus pentasulfide in boiling xylene.¹²²



¹²⁵ F. C. James and D. Krebs, *Phosphorus Sulfur* 6, 143 (1979).

Heteroadamantane

TADASHI SASAKI

*Institute of Applied Organic Chemistry, Faculty of Engineering,
Nagoya University, Nagoya, Japan*

| | |
|--|-----|
| I. Introduction | 80 |
| II. Heteroadamantanes Involving Nitrogen | 81 |
| A. Monoazaadamantanes | 81 |
| 1. 1-Azaadamantanes | 82 |
| 2. 2-Azaadamantanes | 86 |
| B. Diazaadamantanes | 88 |
| 1. 1,3-Diazaadamantanes | 88 |
| 2. 2,6-Diazaadamantanes | 92 |
| C. Triazaadamantanes | 94 |
| 1. 1,3,5-Triazaadamantanes | 95 |
| 2. 2,4,8-Triazaadamantanes | 97 |
| D. Polyazaadamantanes | 98 |
| III. Heteroadamantanes Involving Oxygen | 98 |
| A. Monooxaadamantanes | 98 |
| 1. Synthesis | 98 |
| 2. Chemistry and Applications | 104 |
| B. Dioxadamantanes | 104 |
| 1. 2,4-Dioxadamantanes | 104 |
| 2. 2,6-Dioxadamantanes | 105 |
| C. Trioxadamantanes | 106 |
| 1. 2,4,10-Trioxadamantanes | 106 |
| 2. 2,4,9-Trioxadamantanes | 108 |
| 3. 2,4,6-Trioxadamantanes | 109 |
| D. Polyoxadamantanes | 110 |
| Synthesis | 110 |
| IV. Heteroadamantanes Involving Sulfur | 111 |
| A. Monothiaadamantanes | 111 |
| 1. Synthesis | 111 |
| 2. Chemistry and Applications | 112 |
| B. Dithiaadamantanes | 113 |
| 1. 2,6-Dithiaadamantanes | 113 |
| 2. 2,4-Dithiaadamantanes | 113 |
| C. Trithiaadamantanes | 114 |
| D. Tetrathiaadamantanes | 114 |
| 2,4,6,8-Tetrathiaadamantanes | 114 |

| | |
|--|-----|
| E. Pentathiaadamantanes | 116 |
| F. Hexathiaadamantanes | 117 |
| 1. Synthesis | 117 |
| 2. Chemistry and Applications | 117 |
| V. Heteroadamantanes Involving Two or More Heteroatoms | 118 |
| A. Azaoxaadamantanes | 118 |
| 1. Synthesis | 118 |
| 2. Chemistry and Applications | 122 |
| B. Azathiaadamantanes | 123 |
| 1. Synthesis | 123 |
| 2. Chemistry and Applications | 125 |
| C. Oxathiaadamantanes | 126 |
| Synthesis | 126 |

I. Introduction

Adamantane, which possesses a unique rigid ring system composed of three fused-chair cyclohexane rings, constitutes the smallest repeating unit of the diamond lattice. A heteroadamantane is defined as an adamantane derivative possessing one or more heteroatoms in the adamantane skeleton. The only naturally occurring heteroadamantane is thiaadamantane, which was found in a high-boiling fraction of tar oil from Iranian kerosene.¹⁻³ (The presence of thiaadamantane in tar oil is not surprising, considering the fact that natural oil contains sulfur and adamantane, though in trace quantities. The first synthetic heteroadamantane, 1,3,5,7-tetramethyl-2,4,6,8,9,10-hexathiaadamantane, was prepared from zinc chloride and thioacetic acid in 1886,⁴ and the second one from bromine and thioacetic acid in 1895,⁵ followed by the third from acetyl chloride and liquid hydrogen sulfide.⁶ Also, 2,4,6,8-tetrathiaadamantane and its bridgehead substituted derivatives have been known for a long time, but as incorrect structures.^{7,8} Incorrect structure assignments also were made e.g., for tetramethylhexathiaadamantane. The present correct structures 2,4,6,8-tetrathiaadamantane^{9,10} and 1,3,5,7-tetramethyl-2,4,6,8,9,10-hexathiaadamantane¹¹ were proposed by Predga. Mod-

¹ S. F. Birch, T. V. Cullum, R. A. Dean, and R. L. Denyer, *Nature (London)* **170**, 629 (1953).

² S. F. Birch, *J. Inst. Pet.* **39**, 185 (1953) [*CA* **47**, 10212 (1953)].

³ S. F. Birch, T. V. Cullum, R. A. Dean, and R. L. Denyer, *Ind. Eng. Chem.* **47**, 114 (1955).

⁴ J. Bongartz, *Ber. Dtsch. Chem. Ges.* **19**, 2182 (1886).

⁵ P. Candiani, *Gazz. Chim. Ital.* **25**, 81 (1895).

⁶ R. W. Borgeson and J. A. Wilkinson, *J. Am. Chem. Soc.* **51**, 1455 (1929).

⁷ F. Leteur, *C. R. Acad. Sci.* **133**, 48 (1901).

⁸ E. Fromm and P. Ziersch, *Ber. Dtsch. Chem. Ges.* **39**, 3599 (1906).

⁹ A. Fredga and A. Brändström, *Ark. Kemi, Mineral. Geol.* **26B**, 4 (1948) [*CA* **44**, 7243 (1950)].

¹⁰ A. Fredga and A. Brändström, *Ark. Kemi* **1**, 197 (1949) [*CA* **44**, 3898 (1950)].

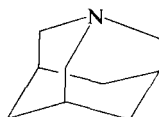
¹¹ A. Fredga and H. Bauer, *Ark. Kemi* **2**, 113 (1951).

ern methods of structural determination confirm these assignments.¹²⁻¹⁷ The chemistry of heteroadamantane is reviewed from different points of view,¹⁸⁻²¹ and is historically documented in reviews of the chemistry of adamantane^{22,23} and briefly in a monograph of adamantane.²⁴ The chemistry of heteroadamantane is just as substantial and diverse by comparison to that of adamantane as is the chemistry of aromatic relative to heteroaromatic compounds. As a heteroatom, almost all of the elements in groups IV, V, and VI can be incorporated into the adamantane skeleton, and even wholly carbon-free versions of the systems are known. In this review, however, heteroadamantanes are confined to molecules containing nitrogen, oxygen, sulfur, and combinations thereof. Additional information of other types of heterocompounds may be obtained by consulting several references.^{19,22,24,25} The compounds in this review are arranged according to types of heteroatoms. The literature is surveyed up to the middle of 1980 as covered by *Chemical Abstracts*.

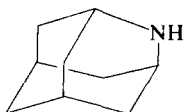
II. Heteroadamantanes Involving Nitrogen

A. MONOAZAADAMANTANES

Two adamantane skeletons containing a single nitrogen are possible; 1-aza- (1) and 2-azaadamantane (2). Both parent compounds and their derivatives have been known for a long time.



(1)



(2)

¹² R. L. Martin and I. M. Stewart, *Nature (London)* **210**, 522 (1966).

¹³ K. Olsson, *Ark. Kemi* **26**, 435 (1967) [*CA* **66**, 104993 (1967)].

¹⁴ K. Olsson, *Ark. Kemi* **26**, 465 (1966).

¹⁵ C. G. Barraclough, R. L. Martin, and I. M. Stewart, *Aust. J. Chem.* **22**, 891 (1969).

¹⁶ M.-O. Hedblom and K. Olsson, *Ark. Kemi* **32**, 309 (1970).

¹⁷ W. Uhle and K. Hartke, *Arch. Pharm. (Weinheim Ger.)* **304**, 42 (1971).

¹⁸ B. M. Michajlov and L. S. Bianchetti, *Vses. Khim. O-vo*, **12**, 77 (1967).

¹⁹ G. Gelbard, *Ann. Chim. (Paris)* **4**, 331 (1969).

²⁰ T. Sasaki, *Kagaku no Ryoiki* **25**, 27 (1971).

²¹ Z. Kafka and V. Galik, *Chem. List* **72**, 509 (1978).

²² H. Stetter, *Angew. Chem.* **66**, 217 (1954); **74**, 361 (1962).

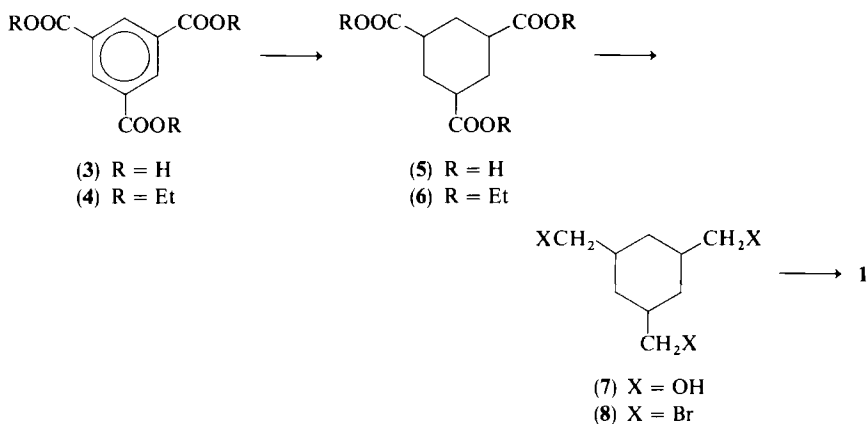
²³ R. C. Fort, Jr. and P. von R. Schleyer, *Chem. Rev.* **64**, 277 (1964).

²⁴ R. C. Fort, Jr. *Adamantane*. Dekker, New York, 1976.

²⁵ T. Sasaki, *Heterocycles* **13**, 531 (1979).

1. 1-Azaadamantanes

a. *Synthesis*. The earliest approaches to **1** by Fusco,^{26,27} Lukes,^{28,29} and Newman³⁰ all started with trimesic acid (**3**). Reduction of the acid (**3**) or its ester (**4**) afforded cyclohexane derivatives **5** or **6**. Lithium aluminum hydride (LAH) reduction of **6** to alcohol **7** and subsequent conversion to bromide **8** followed. Cyclization to **1** as a key step was carried out on **7** with ammonia in the presence of aluminum oxide or on **8** with ammonia (Scheme 1). In order to obtain **1** in good yield, cyclohexane derivatives **7** and **8** have to adopt a conformation with all substituents axial. This is difficult and causes low yields. Furthermore, a big difference in leaving group behavior provides another problem for this synthesis.³¹



SCHEME 1

A different approach to **1** is available^{32,33} for somewhat larger quantities in good yields. The procedure (Scheme 2) is based upon the condensation of ethyl β -bromomethacrylate (**9**) or its precursor, diethyl β,β' -dibromoisobutyrate, with the pyrrolidine enamine (**10**) of *N*-toluene-*p*-sulfonylpiperid-4-one to afford the bicyclic intermediate (**11**). If the carbonyl group is modified

²⁶ R. Fusco and G. Bianchetti, *CA* **49**, 6284 (1955).

²⁷ R. Fusco and G. Bianchetti, *Gazz. Chim. Ital.* **86**, 500 (1956).

²⁸ R. Lukes and V. Galik, *Chem. Listy* **48**, 858 (1954).

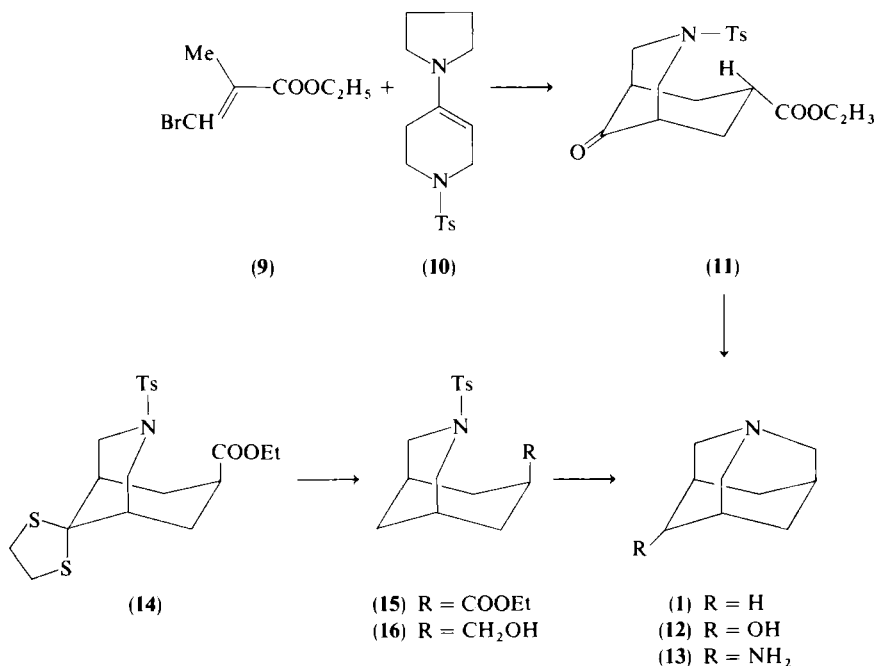
²⁹ R. Lukes and V. Galik, *Collect. Czech. Chem. Commun.* **19**, 712 (1954).

³⁰ S. Newman and H. S. Lowrie, *J. Am. Chem. Soc.* **76**, 4598 (1954).

³¹ V. Galik, Z. Kafka, M. Safar, and S. Landa, *Collect. Czech. Chem. Commun.* **39**, 895 (1974).

³² W. N. Speckamp, J. Dijkink, and H. O. Huisman, *J. C. S. Chem. Commun.*, 196, 197 (1970).

³³ A. W. J. D. Dekkers, W. N. Speckamp, and H. O. Huisman, *Tetrahedron Lett.*, 489 (1971).



SCHEME 2

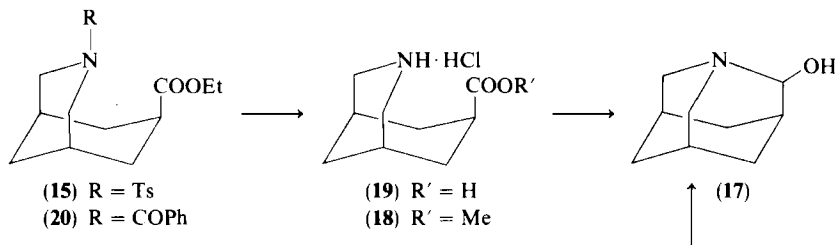
rather than eliminated, 4-substituted 1-azaadamantane derivatives such as **12** ($\text{R} = \text{OH}$) and **13** ($\text{R} = \text{NH}_2$) are obtained. Elimination of the carbonyl group is based on Raney nickel reduction of thioketal **14** to **15**. Final cyclization of alcohol **16** to **1** proceeds in an acidic medium. The only disadvantage of this procedure is that both starting materials, **9** and **10**, are themselves the products of a multistep sequence of reactions: **9** is obtained from formaldehyde and malonic ester,³⁴ whereas **10** is prepared via acid hydrolysis of the corresponding nitrile, which, in turn, is obtained by addition of acrylonitrile to ammonia and tosylation of the subsequently formed dinitrile. This method is applicable to the synthesis of new cinchona and quinine analogs.³⁵ 1-Aza-2-hydroxyadamantane (**17**) is obtained by reductive (H_2/Pd) cyclization of the ester (**18**) in toluene, starting from **15** via the acid (**19**), while direct conversion of *N*-benzoyl derivative **20** affords only 4.5% of **17**.³⁶

Some 3,5,7-trinitro-1-azaadamantane derivatives (**21**, **22**, **23**) are obtained from the corresponding 2,4,6-trinitrobenzene derivatives (**24**, **25**, **26**) via their

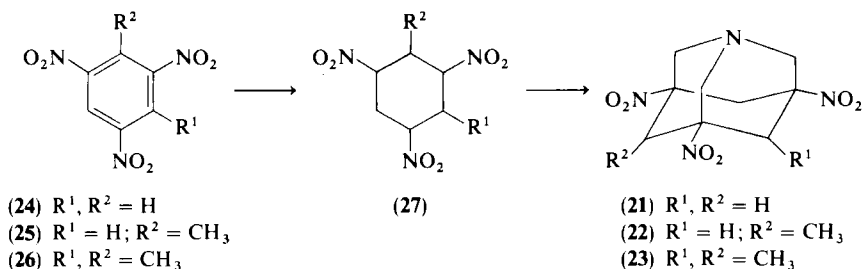
³⁴ A. F. Ferris, *J. Org. Chem.* **20**, 780 (1955).

³⁵ W. N. Speckamp and J. Dijkink, *Heterocycles* **2**, 291 (1974).

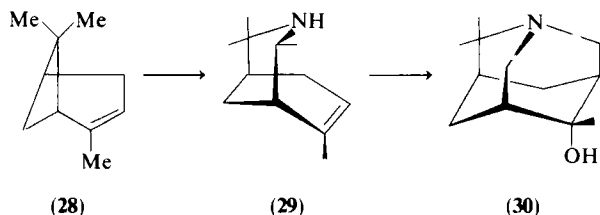
³⁶ H. Stetter and W. Reinartz, *Chem. Ber.* **105**, 2777 (1972).



NaBH₄-reduced cyclohexane derivatives (27). Cyclization of 27 to 21–23 is carried out with ammonia and formaldehyde.^{37–39} A convenient two-step



synthesis of substituted 1-azaadamantanes from α -pinene was recently published.⁴⁰ Solvomercuration–demercuration of α -pinene (28) in the presence of acetonitrile, followed by *in situ* borohydride reduction leads to 2,2,4,6-tetramethyl-3-azabicyclo[3.3.1]non-6-ene (29), which is readily cyclized with aqueous formaldehyde in acid to 4,8,8-trimethyl-4-hydroxy-1-azaadamantane (30) in 88% yield. Here, 29 is a versatile synthon for the one-step synthesis of substituted 1-azaadamantanes via an iminium intermediate. The ready accessibility of α -pinene renders the synthesis both convenient and



³⁷ T. Severin, D. Batz, and H. Kramer, *Chem. Ber.* **104**, 950 (1971).

³⁸ G. D. Georgievskaya, M. D. Boldyrev, and L. I. Bagal, *Zh. Org. Khim.* **7**, 1681 (1971).

³⁹ V. A. Sokolova, M. D. Boldyrev, M. D. Gidasov, and T. N. Timofejeva, *Zh. Org. Khim.* **8**, 1243 (1972).

⁴⁰ B. Delpéch and Q. Khuong-Huu, *J. Org. Chem.* **43**, 4898 (1978).

inexpensive and it opens a way to the synthesis of various other azaadamantanes.

b. *Chemistry and Applications.* Because of interest in bridgehead components the relative reactivity of a cyclized cage amine versus an open-chain tertiary amine was discussed with reference to the thermal and photochemical radical bromination of 1-azaadamantane; the influence of the nitrogen atom interaction on the reactivity of the secondary and tertiary cage hydrogens of 1-azaadamantane is examined.⁴¹⁻⁴³ Crystallographic data are given for 1-azaadamantane.⁴⁴ Isotropic ¹³C paramagnetic shifts for 1-azaadamantane coordinated with paramagnetic nickel(II) acetylacetonate are observed in the completely proton-decoupled ¹³C-NMR spectra.⁴⁵ The conformational dependence of the contact shifts for various protons in 1-azaadamantane is determined by 220-MHz NMR and the results are discussed in relation to the modes of electron-spin distribution through the σ -skeleton.⁴⁶ Calculations of the extended Hückel type are used to discuss the effect of through-bond interaction on a stabilized bridged ion of 1-azaadamantane.⁴⁷ The vertical lone-pair ionization potentials $I_v(n)$ of 1-azaadamantane were determined by photoelectron spectroscopy.⁴⁸ 1-Azaadamantane has the same concentration-dependent luminescent property as 1-azabicyclo[2.2.2]octane in *n*-hexane.⁴⁹ Nickel-induced PMR contact shifts are determined for the γ and δ protons of 1-azaadamantanes.⁵⁰ 1-Azaadamant-4-one and a number of its derivatives, in which the carbonyl function is modified, show absorptions in the near-UV region which are attributed to a σ -coupled transition. Absorption and emission spectroscopy show this transition to be charge transfer in character and to derive its intensity mainly from a local π - π^* transition in the modified carboxyl group. From the relative basicities and the IR and ¹³C NMR spectra it is concluded that the amount of charge transfer in the electronic ground state is very small for the compounds studied.⁵¹ Photoelectron spectra of 1-azaadamant-4-one, 1-azaadamant-4-methylene, and 1-azaadamantane are described in comparison with those

⁴¹ A. W. J. D. Dekkers, J. W. Verhoeven, and W. N. Speckamp, *Tetrahedron* **29**, 1691 (1973).

⁴² W. N. Speckamp, J. Dijkink, and A. W. J. D. Dekkers, *Tetrahedron Lett.*, 1853 (1974).

⁴³ W. N. Speckamp and A. W. J. D. Dekkers, *Tetrahedron Lett.*, 1857 (1974).

⁴⁴ J. Bauer, *Sb. Vys. Sk. Chem.-Technol. Praha* **1**, 145 (1957).

⁴⁵ I. Morishima, K. Okada, T. Yonezawa, and K. Goto, *J. Am. Chem. Soc.* **93**, 3922 (1971).

⁴⁶ I. Morishima, K. Okada, M. Ohashi, and M. Yonezawa, *J. C. S. Chem. Commun.*, 33 (1971).

⁴⁷ R. Gleiter, R. Hoffmann, and W. D. Stohrer, *Chem. Ber.* **105**, 8 (1972).

⁴⁸ G. Bieri and E. Heilbronner, *Helv. Chim. Acta* **57**, 546 (1974).

⁴⁹ A. M. Halpern and E. Maratos, *J. Am. Chem. Soc.* **94**, 8273 (1972).

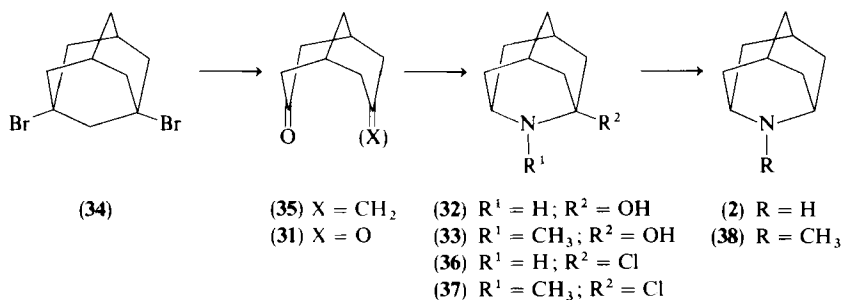
⁵⁰ G. R. Underwood and H. S. Friedman, *J. Am. Chem. Soc.* **96**, 4089 (1974).

⁵¹ A. W. J. D. Dekkers, J. W. Verhoeven, and W. N. Speckamp, *Tetrahedron* **29**, 1961 (1973).

of the corresponding adamantane analogs; in the 1-azaadamantane derivatives a through-bond interaction between the nitrogen lone pair and the 4-substituent is observed. This through-bond interaction is discussed in relation to the σ -coupled transition observed in the electron absorption spectra of 1-azaadamantane derivatives and in relation to their basicities both in solution and in the gas phase.⁵² The structure of a bridgehead aminium radical of 1-azaadamantane is presented on the basis of its electron spin resonance spectrum.⁵³ Paper chromatography of 1-azaadamantane and its quaternary salt is studied in various solvent systems.⁵⁴ The Kováts indices and the relative elution volumes are determined for 1-azaadamantane on the stationary phases.⁵⁵ 1-Azaadamantane is used as a catalyst in the 1,3-rearrangement (tautomerization) of 1-methylindene.⁵⁶ The Hofmann–Löffler–Freitag and Hofmann degradation reactions have been applied to 1-azaadamantane.⁵⁷

2. 2-Azaadamantanes

a. *Synthesis.* 2-Azaadamantane seems to be somewhat more readily available than 1-azaadamantane. The first approach to **2** was reported in 1964 by Stetter *et al.*⁵⁸ The key steps of the reaction are the reductive amination by NH_3 or CH_3NH_2 and H_2/Pt and the spontaneous cyclization of bicyclo[3.3.1]nona-3,7-dione (**31**) to 1-hydroxy-2-azaadamantane ($\text{R} = \text{H}$, **32**; $\text{R} = \text{CH}_3$, **33**). Dione **31** is obtained by base-promoted fragmentation of 1,3-dibromoadamantane (**34**) followed by ozonolysis. The 1-hydroxyl group is removed by chlorination to give **36** or **37** with thionyl chloride. Reduction yields **2** or **38**.



⁵² C. W. Worrell, J. W. Verhoeven, and W. N. Speckamp, *Tetrahedron* **30**, 3525 (1974).

⁵³ W. C. Danen and R. C. Richard, *J. Am. Chem. Soc.* **97**, 2303 (1975).

⁵⁴ Z. Kafka, M. Šafář, and V. Galik, *Collect. Czech. Chem. Commun.* **39**, 3268 (1974).

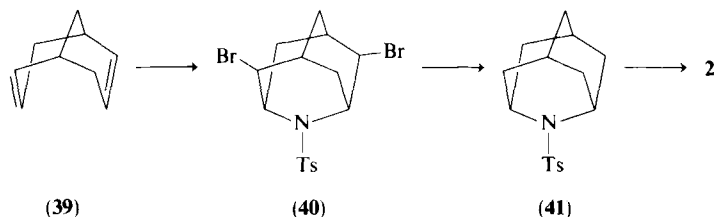
⁵⁵ M. Šafář, V. Galik, and Z. Kafka, *Collect. Czech. Chem. Commun.* **40**, 3334 (1975).

⁵⁶ L. Meurling, *CA* **82**, 138957 (1975).

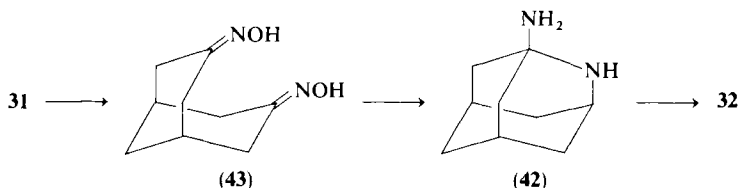
⁵⁷ R. E. Partch, *Diss. Abstr.* **24**, 2696 (1964).

⁵⁸ H. Stetter, P. Tacke, and J. Gartner, *Chem. Ber.* **97**, 3480 (1964).

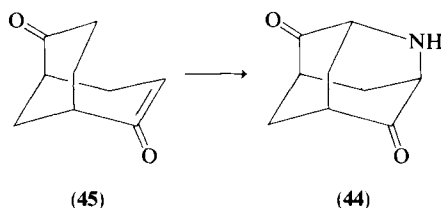
An improved procedure^{59,60} uses bicyclo[3.3.1]nona-2,6-diene (**39**) instead of dione **31**. Addition of *N,N*-dibromo-*p*-toluenesulfonamide to **39** gives **40** which is debrominated to **41** and hydrolyzed to **2**.



1-Amino-2-azaadamantane (**42**) is obtained by catalytic reduction (H_2/PtO_2) of the dioxime (**43**) derived from **31**. The amino group is readily replaced with a hydroxyl group by diazotization affording **32**.⁶¹⁻⁶³



2-Azaadamantan-4,8-dione (**44**) is also obtained from bicyclo[3.3.1]nona-2,6-dione (**45**) by bromination and subsequent amination.⁶¹



b. Chemistry and Applications. 2-Azaadamantan-4,8-dione (**44**) is a potential precursor of various derivatives.⁶⁴ *N*-Methyl-2-azaadamantane (**38**) has been studied to determine steric and other factors influencing the quarternization of tertiary amines. For the reaction of **38** with methyl iodide in acetonitrile, $k_2 = 73.7 \times 10^{-4}$ liter/mol/sec at 0°C , $\Delta H = 11.8$ kcal/mol, and

⁵⁹ H. Stetter and K. Heckel, *Tetrahedron Lett.*, 1907 (1972).

⁶⁰ H. Stetter and K. Heckel, *Chem. Ber.* **106**, 339 (1973).

⁶¹ A. R. Gagneux and R. Meuer, *Tetrahedron Lett.*, 1365 (1969).

⁶² J. R. Geigy, British Patent 1,096,060 [*CA* **69**, 27268 (1968)].

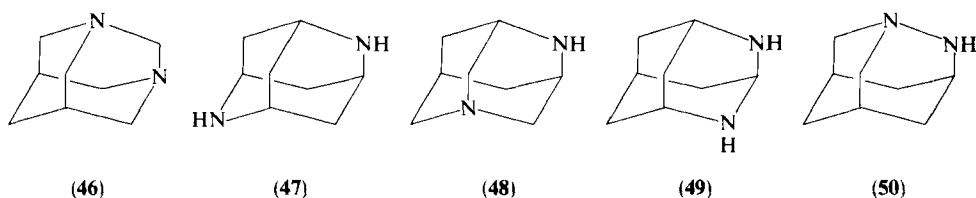
⁶³ J. R. Geigy, French Patent 1,500,681 [*CA* **69**, 106575 (1968)].

⁶⁴ G. Snatzke and H. Seidler, *Tetrahedron Lett.*, 5135 (1969).

$\Delta S = -25.8$ cal/mol/deg, while $k_2 = 119 \times 10^{-4}$ liter/mol/sec at 0°C , $\Delta H = 10.2$ kcal/mol, and $\Delta S = -30.7$ cal/mol/deg for 4-*t*-butyl-*N*-methylpiperidine and methyl iodide. From these data, quaternization is concluded to proceed normally with equatorial attack and is slowed by interactions encountered by the substituent on nitrogen as it becomes axial in the transition state. The rigid adamantane skeleton makes these interactions more severe and consequently, it reacts more slowly than an unbridged model.⁶⁵ Guanidine derivatives,⁶⁶ antiviral agents containing 2-azaadamantanes,⁶⁷ antiviral 2-aza-2-adamantyl carboxyamides,⁶⁸ and *N*-[2-(2-azaadamant-2-yl)ethyl]guanidine antihypertensive agents⁶⁹ are patented.

B. DIAZAADAMANTANES

There are five possible isomers of diazaadamantanes, **46**–**50**; of these, only 1,3-diaza- with two nitrogens at both bridgeheads (**46**) and 2,6-diazaadamantanes with two nitrogens in separate bridges (**47**) are known.



1. 1,3-Diazaadamantanes

a. *Synthesis*. Two different approaches to **46** were reported by two different research groups in 1955.^{71,72}

The final step to **46** is cyclocondensation of 3,7-diazabicyclo[3.3.1]nonane (**51**), bispidine⁷⁰, with formaldehyde. There are two different approaches to **51**: (i) a pyridine is converted to a piperidine and (ii) the double Mannich or Robinson–Schöpf condensation of ketone **52** with formaldehyde and primary amines affords 1,5-disubstituted 3,7-diazabicyclo[3.3.1]nonan-9-one (**53**), bispidone, from which 5,7-disubstituted 1,3-diazaadamantan-6-one (**61**) is derived. Route (i) is adopted by Galinovsky and Langer,⁷¹ Stetter and

⁶⁵ J.-L. Inbach, A. R. Katritzky, and B. A. Kolinski, *J. Chem. Soc. B*, 556 (1966).

⁶⁶ J. R. Geigy, Netherlands Patent Appl. 6,607,597 (1966) [*CA* **67**, 116556 (1967)].

⁶⁷ A. Gagneux, Ger. Offen. 1,802,641 (1969) [*CA* **71**, 116556 (1969)].

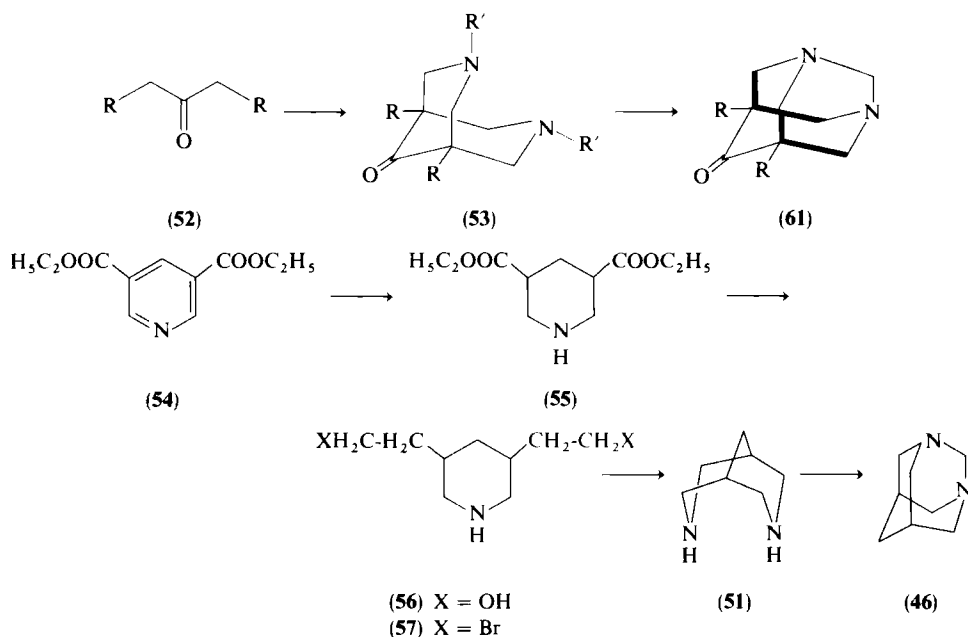
⁶⁸ A. Gagneux, Ger. Offen. 1,802,640 (1969) [*CA* **71**, 124257 (1969)].

⁶⁹ A. Gagneux, U.S. Patent 3,549,764 (1970) [*CA* **74**, 125474 (1971)].

⁷⁰ A. Chiavarelli, F. Toffler, and D. Misiti, *Ann. Ist. Super. Sanita* **4**, 157 (1968) [*CA* **70**, 68574 (1969)].

⁷¹ F. Galinovsky and H. Langer, *Monatsh. Chem.* **86**, 449 (1955).

Hennig,⁷² and Bohlmann and Ottawa⁷³ and route (ii) by Stetter *et al.*^{74–76} and Chiavarelli *et al.*^{77–80} In route (i), the starting material is pyridine-3,5-dicarboxylate (**54**). One example provided by Galinovsky and Langer⁷¹



employs reduction of **54** with H_2/PtO_2 to give piperidine-3,5-dicarboxylate (**55**), which is further reduced with LAH to the alcohol (**56**). This is converted to the bromide (**57**) with hydrogen bromide followed by treatment with ammonia to afford **51**.

A variation of this procedure devised by Galik and Landa⁸¹ starts with propane-1,1,3,3-tetracarboxylate (**58**) instead of **54**. LAH reduction of **58** affords the alcohol (**59**). After converting **59** to the bromide (**60**), **51** is obtained

⁷² H. Stetter and H. Hennig, *Chem. Ber.* **88**, 789 (1955).

⁷³ F. Bohlmann and N. Ottawa, *Chem. Ber.* **88**, 1828 (1955).

⁷⁴ H. Stetter, J. Schäfer, and K. Dieminger, *Angew. Chem.* **70**, 52 (1958).

⁷⁵ H. Stetter, J. Schäfer, and K. Dieminger, *Chem. Ber.* **91**, 598 (1958).

⁷⁶ H. Stetter, K. Dieminger, and E. Rauscher, *Chem. Ber.* **92**, 2057 (1959).

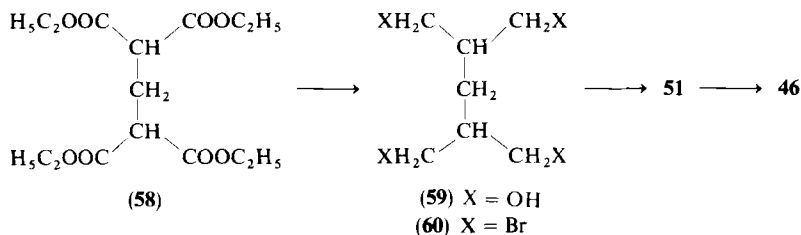
⁷⁷ S. Chiavarelli, F. Toffler, P. Mazzero, and L. Gramiccioni, *Farmaco, Ed. Sci.* **23**, 360 (1968) [*CA* **69**, 52115 (1969)].

⁷⁸ S. Chivarelli, F. Toffler, L. Gramiccioni, and G. P. Valsecchi, *Gazz. Chim. Ital.* **98**, 1126 (1968).

⁷⁹ R. Landivittory, G. Settimj, F. Gatta, N. Sarti, and S. Chivarelli, *Gazz. Chim. Ital.* **97**, 1294 (1967).

⁸⁰ D. Misiti and S. Chivarelli, *Gazz. Chim. Ital.* **96**, 1696 (1966).

⁸¹ V. Galik and S. Landa, *Collect. Czech. Chem. Commun.* **38**, 1101 (1973).



upon treatment with ammonia. Route (ii) in comparison with route (i) has an advantage of more ready accessibility. However, as a consequence of the use of a substituted ketone, **53** and **61** are bridgehead-substituted.

Diammonium 1,3-diazaadamantan-6-one-5,7-disulfonate is obtained by heating an aqueous solution of diammonium propanone-1,3-disulfonate (prepared easily by sulfonation of acetone with fuming sulfuric acid) and hexamethylenetetramine.⁸² Other several 1,3-diazaadamantan-6-one derivatives are prepared similarly.⁸³⁻⁸⁶

b. *Chemistry and Application.* Kuthan,⁸⁶ Cookson,⁸⁷ and the author⁸⁸ discuss the ultraviolet spectra of 1,5-dialkyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**53**) and 5,7-dimethyl-1,3-diazaadamantan-6-one (**61**); although **53** has no absorption, **61** absorbs strongly at 262 nm ($\epsilon = 3600$). This difference is attributed to σ -coupling. In **61**, the lone pairs on nitrogen are required by the adamantane skeleton to lie almost in the same plane and collinear with the p orbitals of the carbonyl group and the σ -bonds shown as heavy lines. In this orientation, the σ -bonds can couple the lone pairs and the carbonyl, permitting a transition in which n -electron density from nitrogen appears in the π^* orbital of the carbonyl. The most likely orientation of the lone pairs in **53** is axial to avoid steric problems with the methyl, as shown, which places them nearly orthogonal to the carbonyl; thus, no interaction is possible.

Several reactions of 1,3-diazaadamantan-6-one are reported.^{89,90} 1,3-diazaadamantane is oxidized with hydrogen peroxide to give a mixture of bis- and mononitroxides.⁹¹ The reaction of N-methylated 1,3-diazaadaman-

⁸² W. G. Grot, *J. Org. Chem.* **30**, 515 (1965).

⁸³ S. Weiner and D. Ginsburg, *Isr. J. Chem.* **4**, 39 (1966).

⁸⁴ J. Kuthan and J. Paleček, *Collect. Czech. Chem. Commun.* **28**, 2260 (1963).

⁸⁵ J. Kuthan, J. Paleček, and L. Musil, *Z. Chem.* **8**, 229 (1968).

⁸⁶ J. Kuthan, J. Paleček, and L. Musil, *Collect. Czech. Chem. Commun.* **38**, 3491 (1973).

⁸⁷ R. C. Cookson, J. Henstock, and J. Hudec, *J. Am. Chem. Soc.* **88**, 1060 (1966).

⁸⁸ T. Sasaki, S. Eguchi, T. Kiriya, and Y. Sakito, *J. Org. Chem.* **38**, 1648 (1973).

⁸⁹ R. E. Portmann and C. Ganter, *Helv. Chim. Acta* **56**, 1986 (1973).

⁹⁰ Z. Kafka, V. Galik, and M. Safar, *Collect. Czech. Chem. Commun.* **40**, 174 (1975).

⁹¹ R. M. Dupeyre and A. Rassat, French Patent 2,105,005 (1972) [*CA* **78**, 16159 (1973)].

tane prepared from 3,5-diazabicyclo[3.3.1]nonane sulfate under Eschweiler-Clarke reductive methylation conditions is discussed.⁹² The electrochemical oxidation reactions of 2,2-cyclopentamethylene-1,3-diazaadamantane, 4,8-diphenyl-1,3-diazaadamantane, and 4,8-diphenyl-1,3-diazaadamantan-10-one have been investigated using cyclic voltammetry,⁹³ and their PMR data are given.⁹⁴ The electronic spectra of 1,3-diazaadamantane derivatives are given⁹⁵ and their conformations established from IR, PMR, and dipole moment data.⁹⁶ Photoelectron spectra of 1,3-diazaadamantane derivatives are measured and lone pair-lone pair interaction is discussed.⁹⁷ Starting from norpseudopelletierine, syntheses of two monoradical and biradical nitroxides having a 1,3-diazaadamantane skeleton are described and ESR and PMR spectra are measured.⁹⁸ X-ray diffraction data for 2,7-dinitro-6,6-dimethyl-1,3-diazaadamantane are given.⁹⁹

4,8-Diphenyl-1,3-diazaadamantan-10-one is utilized to increase the intrinsic UV sensitivity of diazo copying materials.¹⁰⁰

A deep interest in the pharmacological activity of 1,3-diazaadamantane and its derivatives has been spurred by their toxicity.^{83,101-113} They are as

⁹² E. E. Smissman and J. A. Weis, *J. Heterocycl. Chem.* **5**, 405 (1968).

⁹³ S. F. Nelsen and P. J. Hintz, *J. Am. Chem. Soc.* **94**, 7114 (1972).

⁹⁴ S. F. Nelsen, P. J. Hintz, and R. T. Landis, *J. Am. Chem. Soc.* **94**, 7105 (1972).

⁹⁵ J. Kuthan, J. Palecek, and L. Musil, *Collect. Czech. Chem. Commun.* **39**, 750 (1974).

⁹⁶ P. Scheiber and K. Kador, *Acta Chim. Acad. Sci. Hung.* **84**, 193 (1975) [*CA* **82**, 124595 (1975)].

⁹⁷ S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.* **96**, 7930 (1974).

⁹⁸ R. M. Dupeyre, A. Rassat, and J. Ronzand, *J. Am. Chem. Soc.* **96**, 6559 (1974).

⁹⁹ N. S. Zefirov and N. V. Averina, U.S.S.R. Patent 266759 (1972) [*CA* **78**, 111128 (1973)].

¹⁰⁰ E. Inoue, H. Kokado, and T. Yamase, Ger. Offen. 2,215,474 (1973) [*CA* **80**, 54530 (1974)].

¹⁰¹ V. G. Longo, B. Silvestrini, and D. Bovet, *J. Pharmacol. Exp. Ther.* **126**, 41 (1959) [*CA* **53**, 22464d (1959)].

¹⁰² V. G. Longo, *J. Pharmacol. Exp. Ther.* **132**, 240 (1961) [*CA* **55**, 17891 (1961)].

¹⁰³ K. Klemen and D. Bovet, *Acta Physiol. Acad. Sci. Hung.* **19**, 143 (1961) [*CA* **55**, 26266h (1961)].

¹⁰⁴ V. S. Longo, *Boll. Soc. Ital. Biol. Sper.* **35**, 2035 (1959) [*CA* **57**, 7854g (1962)].

¹⁰⁵ S. Chiavarelli and L. V. Fennoy, *J. Org. Chem.* **26**, 4895 (1961).

¹⁰⁶ J. L. McGaugh, C. W. Thompson, W. H. Westbrook, and W. J. Hudspeth, *Psychopharmacologia* **3**, 352 (1962) [*CA* **60**, 3390e (1964)].

¹⁰⁷ S. Chiavarelli, L. V. Fennoy, G. Settimij, and L. Dezarani, *J. Med. Pharm. Chem.* **5**, 1293 (1962) [*CA* **59**, 631h (1963)].

¹⁰⁸ I. Setniker, W. Murmann, and M. J. Magistretti, *Arch. Int. Pharmacodyn. Ther.* **113**, 364 (1962) [*CA* **58**, 845e (1963)].

¹⁰⁹ D. Bovet and D. V. Longo, *Reg. Neurochem. Reg. Chem., Physiol. Pharmacol. Nerv. Syst., Proc. Int. Neurochem. Symp., 4th*, 1960, 456 (1961) [*CA* **60**, 6058 (1964)].

¹¹⁰ R. L. Vittori, G. Settimij, E. Gatta, N. Sarti, and S. Chivarelli, *Gazz. Chim. Ital.* **97**, 1294 (1967).

¹¹¹ D. R. Curtius, R. Hosli, and G. A. R. Johnston, *Nature (London)* **215**, 1502 (1967).

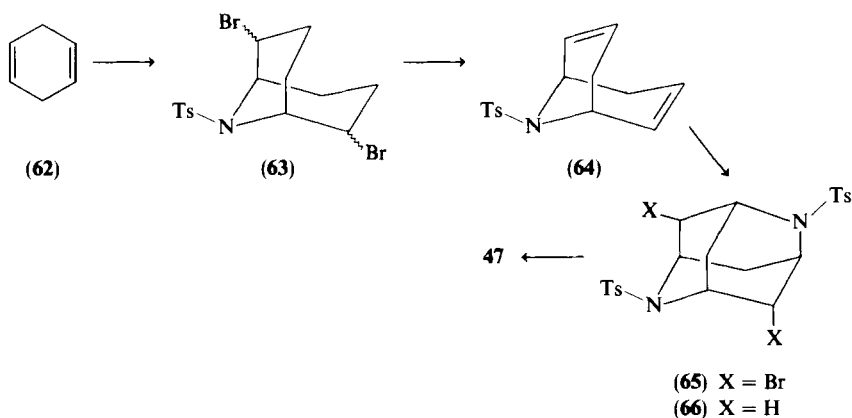
¹¹² G. Chen, *Proc. Soc. Exp. Biol. Med.* **112**, 611 (1963) [*CA* **59**, 12065 (1963)].

¹¹³ D. R. Curtius, *Int. J. Neuropharmacol.* **1**, 239 (1962) [*CA* **60**, 12562 (1964)].

virulent as strychnine and have a similar mode of action, influencing the transmission of nerve impulses to produce a strong convulsant effect.^{101,102} Introduction of phenyl substituents lowers strychnine-like activity and in some 3,4-dimethoxy and 3,4,5-trimethoxy derivatives, the activity disappears completely.¹⁰⁷

2. 2,6-Diazaadamantanes

a. *Synthesis*. Three main approaches to the 2,6-diazaadamantane skeleton are reported by three research groups of Stetter and Heckel,^{59,60,114} Dupeyre and Rassat,¹¹⁵ and Portmann and Ganter.⁸⁹ Stetter's route to **47** starts from 1,5-cyclooctadiene (**62**). The fundamental idea is similar to that given in the sequence **39** → **40** → **41** → **42** for the synthesis of 2-azaadamantane. 9-Tosyl-9-azabicyclo[3.3.1]nona-2,6-diene (**64**), an aza analog of **39** is obtained by pyrolysis of the 2,6-dibromide (**63**), which is prepared by addition of

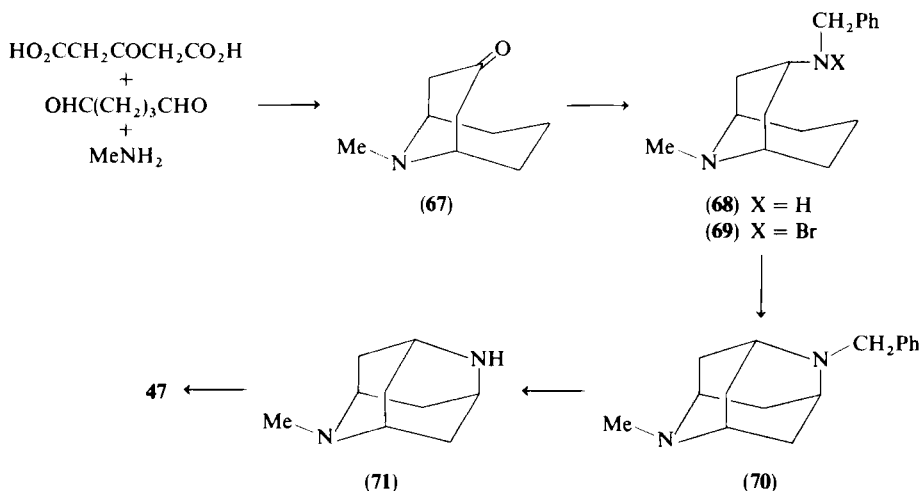


N,N-dibromo-*p*-toluenesulfonamide to **62**. Cyclization of **64** to **65** as a key step is also carried out by using *N,N*-dibromo-*p*-toluenesulfonamide, leading to 4,8-dibromo-2,6-ditosyl-2,6-diazaadamantane (**65**). Reduction of **65** with Raney nickel affords 2,6-ditosyl-2,6-diazaadamantane (**66**) after removal of bromine. Reduction of **66** with sodium in liquid ammonia gives the final product **47**. An approach by Dupeyre and Rassat commences with a Mannich condensation of propane-1,3-dialdehyde, 3-ketoglutaric acid, and monomethylamine, affording 9-methyl-9-azabicyclo[3.3.1]nonan-3-one (**67**). Con-

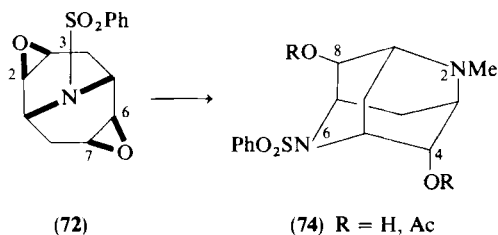
¹¹⁴ H. Stetter and K. Heckel, *Tetrahedron Lett.*, 801 (1972).

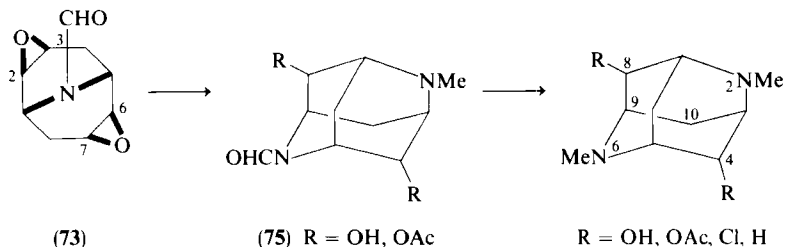
¹¹⁵ R.-M. Dupeyre and A. Rassat, *Tetrahedron Lett.*, 2699 (1973).

densation of **67** with benzylamine and subsequent reduction with Raney nickel gives the 3-benzylamino derivative (**68**). After bromination to give **69**, cyclization of **69** to 2-benzyl-6-methyl-2,6-diazaadamantane (**70**) is carried



out in sulfonic acid. Removal of the benzyl group in **70** by reduction (Pd/C, H_2 affords 6-methyl-2,6-diazaadamantane (**71**). Removal of the methyl group in **71** is carried out by oxidation with potassium permanganate in a basic medium, affording **47**. These two methods have some meaning from preparative points of view; the former can be used to prepare substituted 2,6-diazaadamantane derivatives, in which the possible interaction of the nitrogens with the substituents may be interesting. The latter can be said to be an application of Hofmann-Löffler-Freytag reaction to give **68**. The third approach to the 2,6-diazaadamantane skeleton adopted by Portmann and Ganter⁸⁹ starts from *syn-exo*-diepoxides, (**72** and **73**). The yield for the conversion of **72** to 2-methyl-6-benzenesulfonyl-4,8-dihydroxy-2,6-diazaadamantane (**74**) in methylamine is 98%. Similar conversion of **73** to the diazaadamantane (**75**) gives a 63% yield.

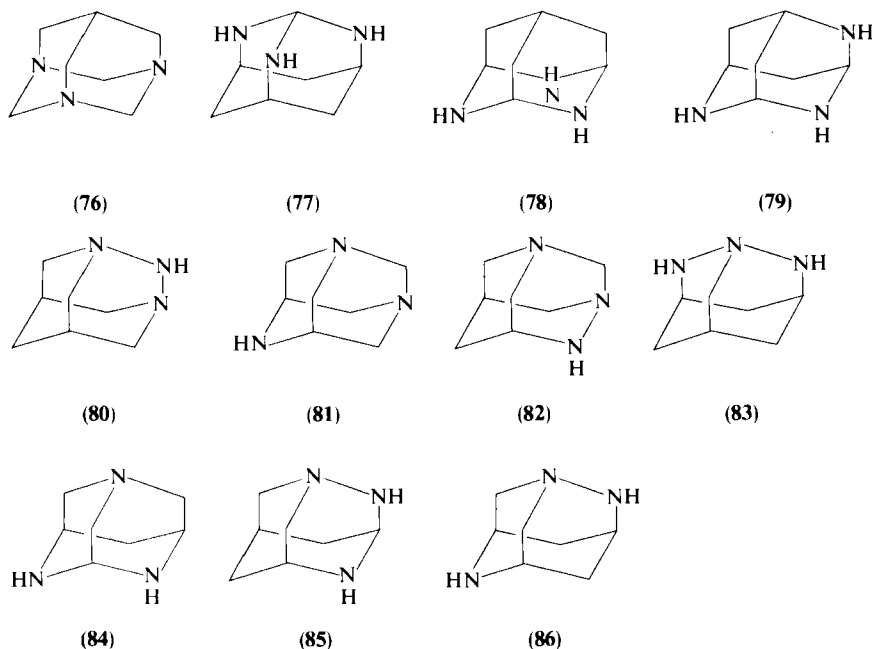




b. *Chemistry and Applications.* Chemistry and applications of 2,6-diazaadamantane derivatives remain unexplored.

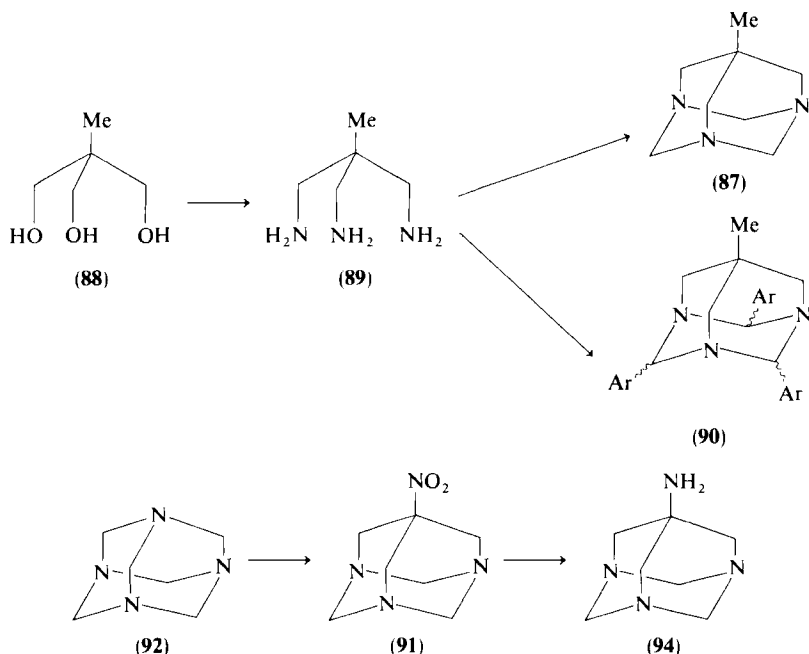
C. TRIAZAADAMANTANES

Of eleven possible triazaadamantanes from **76** to **86**, only two, 1,3,5- with three nitrogens all at the bridgeheads (**76**) and 2,4,8-triazaadamantanes with three nitrogens all at the bridges (**77**) are known. Interestingly, this pattern of substitution is similar to that in diazaadamantanes.



1. 1,3,5-Triazaadamantanes

a. *Synthesis.* The first approach was carried out by Stetter and Bockmann in the synthesis of 7-methyl-1,3,5-triazaadamantane (**87**),¹¹⁶ from 1,1,1-tri(hydroxymethyl)methane (**88**). After several steps **88** is converted to 1,1,1-tri(aminomethyl)ethane (**89**), cyclization of which in the presence of paraformaldehyde affords **87**. When aromatic aldehydes such as 2-pyridylaldehyde are used instead of paraformaldehyde, a 2,4,9-triaryl substituted product (**90**) is obtained.¹¹⁷ 7-Nitro-1,3,5-triazaadamantane (**91**) is prepared by a closely related condensation of 1-nitro-1,1,1-tri(hydroxymethyl)methane with paraformaldehyde in the presence of ammonium acetate.¹¹⁷ Equivalent approaches follow from nitromethane, paraformaldehyde and ammonium acetate,^{118,119} or from hexamethylenetetramine (**92**), nitromethane, and formic acid.^{120,121}



¹¹⁶ H. Stetter and W. Bockmann, *Chem. Ber.* **84**, 834 (1951).

¹¹⁷ D. A. Durham, F. A. Hart, and D. Shaw, *J. Inorg. Nucl. Chem.* **29**, 509 (1967) [*CA* **67**, 100121 (1967)].

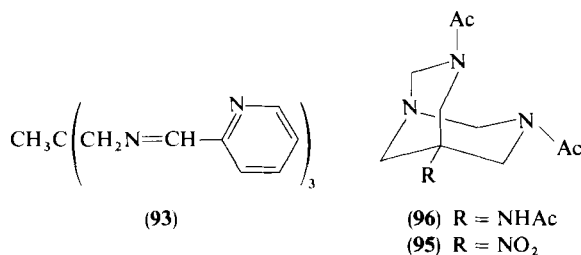
¹¹⁸ N. W. Gabel, U.S. Patent 3,301,854 (1967) [*CA* **67**, 21936h (1967)].

¹¹⁹ V. Galik, M. Safar, Z. Kafka, and S. Landa, *Collect. Czech. Chem. Commun.* **40**, 442 (1975).

¹²⁰ M. Safar, V. Galik, Z. Kafka, and S. Landa, *Collect. Czech. Chem. Commun.* **40**, 2179 (1975).

¹²¹ V. Galik and S. Landa, Czech Patent 163,520 (1975).

b. *Chemistry and Applications.* The 1,3,5-triazaadamantane ring system is subject to facile ring opening like hexamethylenetetramine (**92**). Durham *et al.*¹¹⁷ note that whereas **90** forms stable complexes with lanthanides, it is rapidly opened by aqueous ferrous ion to produce a complex of compound **93**. Hodge¹²² finds both 7-nitro- (**91**) and 7-amino-1,3,5-triazaadamantane (**94**), which is obtained by LAH reduction of **91**,¹¹⁷ react with acetic acid to form ring-opened bicyclic products, **95** and **96**, respectively. Only under comparatively mild conditions is the skeletal integrity maintained as exemplified by reduction of 7-nitro to 7-amino compounds.¹²³⁻¹²⁵



Nielson¹²⁶ reports the synthesis of 7-(*N*-alkylamino)- and 7-(*N,N*-dialkylamino)-1,3,5-triazaadamantanes by reductive alkylation of **94**, which is obtained from **91** by an improved hydrogenation procedure (rhodium-charcoal catalyst, 25.5 psi). Paper chromatography⁵⁴ and the Kováts indices and relative elution volumes of 1,3,5-triazaadamantane derivatives are measured.⁵⁵ 7-Amino-1,3,5-triazaadamantane is used as a vulcanization accelerator.¹²⁷ 7-(*N,N*-Dialkylamino)-1,3,5-triazaadamantanes are utilized as a new class of high-density fuel (DIADAM).¹²⁸ Some 7-substituted 1,3,5-triazaadamantanes have bacteriostatic and fungistatic activity.¹²⁹ 7-Bromo-

¹²² E. B. Hodge, *J. Org. Chem.* **37**, 320 (1972).

¹²³ A. I. Kuznecov, O. T. Burdelev, and B. V. Unkovskij, *Tr. Jubil. Konf.*, 163 (1970) [*CA* **81**, 125638 (1974)].

¹²⁴ V. Galik, Z. Kafka, and M. Safar, *Sb. Vys. Sk. Chem.-Technol. Praze, Technol. Paliv* **D32**, 127 (1976).

¹²⁵ V. Galik, Z. Kafka, and L. Vodicka, *Sb. Vys. Sk. Chem. Technol. Praze, Technol. Paliv* **D36**, 109 (1977).

¹²⁶ A. T. Nielson, *J. Heterocycl. Chem.* **12**, 161 (1975).

¹²⁷ B. V. Unkovskij, I. I. Gridunov, A. I. Kuznecov, A. G. Fedrov, Y. E. Rozental, and E. L. Tarasevic, *Otkrytia, Izobret., Prom. Obraztsy, Tovarnye Znaki* **52**, 43 (1975) [*CA* **83**, 116593 (1975)].

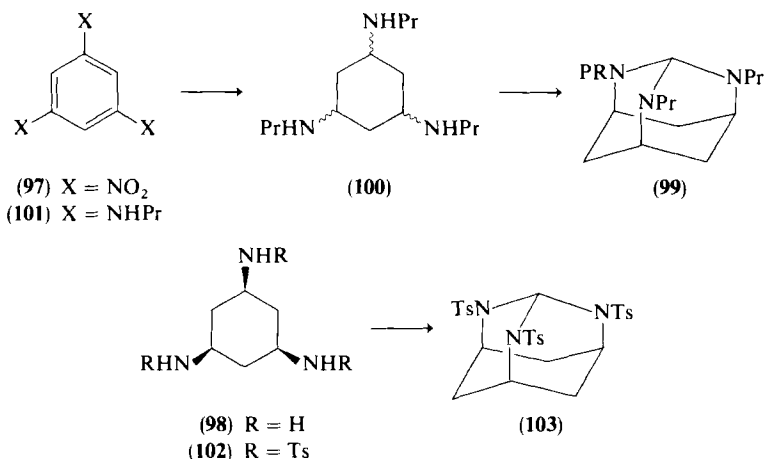
¹²⁸ A. T. Nielson, *Gov. Rep. Announce (U.S.)* **75**, 51 (1975) [*CA* **83**, 63020 (1975)].

¹²⁹ E. B. Hodge and C. D. Hurd, *Ger. Offen.* 1,956,234 (1970) [*CA* **73**, 66630 (1973)].

7-amino-, and 7-nitro-1,3,5-triazaadamantanes are known to exert antiviral activity against influenza A₂ virus *in vitro*.^{130,131}

2. 2,4,8-Triazaadamantanes

a. *Synthesis.* Stetter's approach to the 2,4,8-triazaadamantane ring system^{132,133} starts from 1,3,5-trinitrobenzene (**97**). As explained in the synthesis of 1-azaadamantane (**1**) from trimesic acid (**3**), a key question is how to prepare 1,3,5-triaminocyclohexane (**98**) having a conformation with all amino group axial. For this purpose 2,4,8-tripropyl-2,4,8-triazaadamantane (**99**) is ring-opened by hydrochloric acid. Here, **99** is prepared by thermal cyclization of 1,3,5-tripropylaminocyclohexane (**100**) with orthoformate in rather low yields. Compound **100** is obtained by double reduction of **97** via 1,3,5-tripropylaminobenzene (**101**), first with H₂/Pd in the presence of a mixture of acetic and propionic anhydrides, then with H₂/Ni. Compound **98** is tosylated with tosyl chloride to give the tosylated compound (**102**), cyclization of which with orthoformate yields 2,4,8-tritosyl-2,4,8-triazaadamantane (**103**) in good yields. However, no description is reported about any attempted conversion of **103** to parent **77**, which is expected to undergo ring opening under the hydrolysis conditions.



¹³⁰ S. A. Vickanova, L. V. Gorjunova, L. D. Sipulina, F. A. Badaev, I. A. Kuznecov, O. N. Tolkacev, and B. V. Unkovskii, *Farmakol. Toksikol. (Moscow)* **37**, 76 (1974) [*CA* **81**, 45184 (1974)].

¹³¹ A. F. Frolov, G. I. Danilenko, and J. V. Siraj, *Konf. Adamantane, Kijev*, (1974).

¹³² H. Stetter, D. Theisen, and G. J. Steffens, *Chem. Ber.* **103**, 200 (1970).

¹³³ H. Stetter and J. Bremen, *Chem. Ber.* **106**, 2523 (1973).

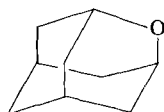
D. POLYAZAADAMANTANES

Only 1,3,5,7-tetraazaadamantane is known. It is also called hexamethylenetetramine (**93**) (HMT), hexamine, aminoform, ammoform, cycloamin, cystogen, formin, uritone, urotropin, and methenamine. It is listed by the last name in the *Merck Index*. It is prepared from formaldehyde and ammonia. The chemistry of this well-known compound is not discussed in this review.

III. Heteroadamantanes Involving Oxygen

A. MONOOXAADAMANTANES

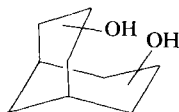
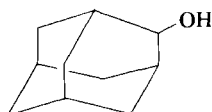
Only one monooxaadamantane skeleton is possible, compound **104**.



(104)

1. Synthesis

Syntheses of the monooxaadamantane skeleton may be classified as follows: (a) addition of electrophiles to bicyclononadiene (**39**); (b) ring closure of bicyclononadione (**31**) or its monomethylene analog (**35**); (c) dehydration of alcohols of the type **105**; (d) radical cleavage of 2-ada-matanol (**106**); (e) miscellaneous.

(105a) 2,6-
(105b) 3,7-

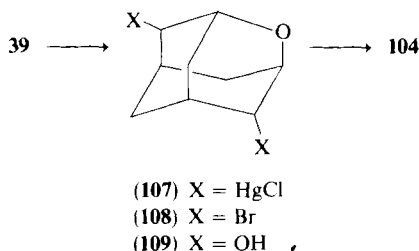
(106)

a. *Addition to 39*. Diene **39** starting material is prepared by LAH reduction of bicyclo[3.3.1]nona-2,6-dione (**45**) to bicyclo[3.3.1]nonan-2,6-diol (**105a**) and subsequent dehydration of **105a** by refluxing in toluene in the presence of boric acid.¹³⁴ Dione **45** is readily prepared from "Meerwein's

¹³⁴ N. V. Averina and N. S. Zefirov, *Zh. Org. Khim.* **5**, 1991 (1969).

ether" by acid hydrolysis.¹³⁵ This route was investigated by Zefirov and his associates.^{134,136-139}

Following this preparation of **39** it is subjected to oxymercuration with mercury acetate and sodium chloride to give 4,8-bischloromercury-substituted 2-oxaadamantane (**107**). Subsequent reduction with sodium borohydride yields **104**.^{134,136}



Another approach is based on the electrophilic halogenation of **39** in the presence of water, affording 4,8-dibromo-2-oxaadamantane (**108**) in 40.6% yield. Boiling **108** with Raney nickel in methanol yields **104**.^{137,138} 4,8-Dihydroxy-2-oxaadamantane (**109**) is obtained by performic acid oxidation of **39**.¹³⁷

b. *Ring Closure of 31*. This procedure by Stetter *et al.*⁵⁸ is based on Raney nickel hydrogenation of **31** with concurrent ring closure to 1-hydroxy-2-oxaadamantane (**110**). The hydroxyl group in **110** is readily removed by bromination to **111** and then by reduction with Raney nickel.

Alkyl Grignard or phenyllithium addition to **31** affords 1-substituted 3-hydroxy-2-oxaadamantane (**112** or **113**). The effect of methyl and phenyl substituents upon the solvolysis reactions is discussed.¹⁴⁰ Attempted enamine formation of **31** with pyrrolidine results in ring closure to 1,3-disubstituted 2-oxaadamantane (**114**).^{141,142}

The monomethylene ketone (**35**), actually a synthetic precursor of **31** as shown by the **34** → **35** → **31** conversion, is convertible to 2-oxaadamantane

¹³⁵ H. Meerwein, *J. Prakt. Chem.* **101**, 161 (1922).

¹³⁶ N. S. Zefirov and N. V. Averina, *Zh. Org. Khim.* **5**, 190 (1969).

¹³⁷ N. S. Zefirov, V. A. Tartakovskii, and N. V. Averina, *Zh. Org. Khim.* **7**, 504 (1971).

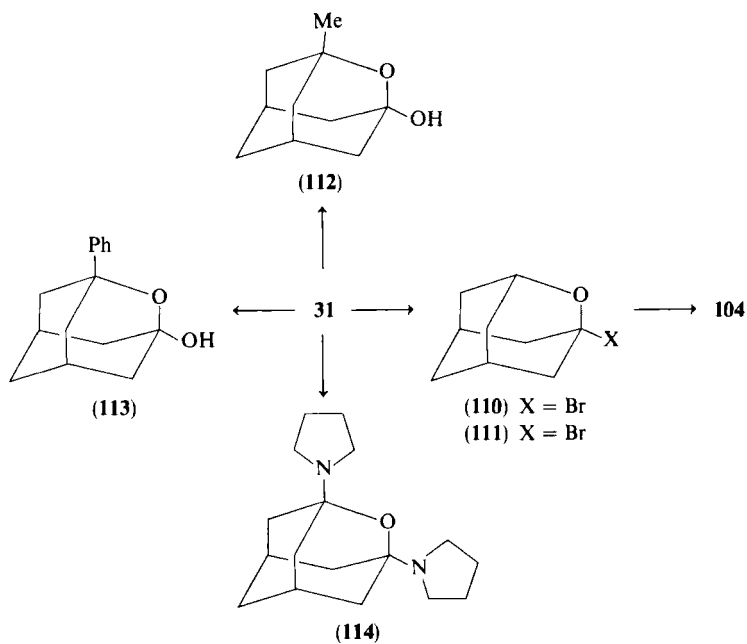
¹³⁸ N. S. Zefirov and N. V. Averina, U.S.S.R. Patent 266,759 (1972) [*CA* **78**, 111128 (1973)].

¹³⁹ N. V. Averina, N. S. Zefirov, P. Kadziauskas, and N. K. Sadovaja, *Zh. Org. Khim.* **11**, 77 (1975).

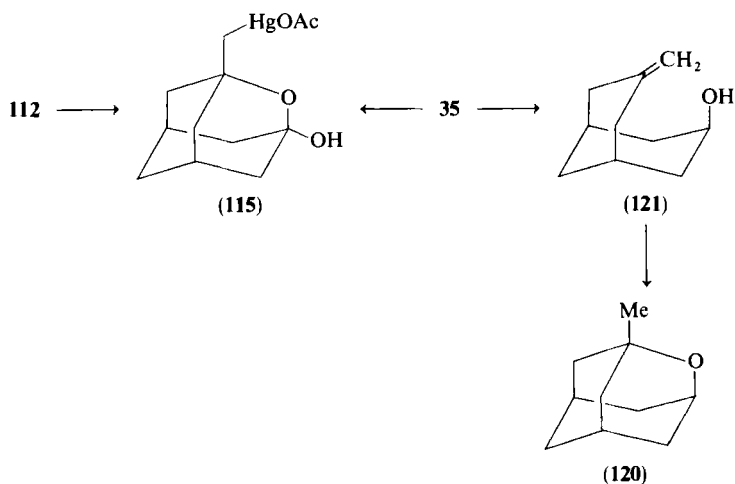
¹⁴⁰ H. Stetter, J. Gartner, and P. Tacke, *Chem. Ber.* **99**, 1435 (1966).

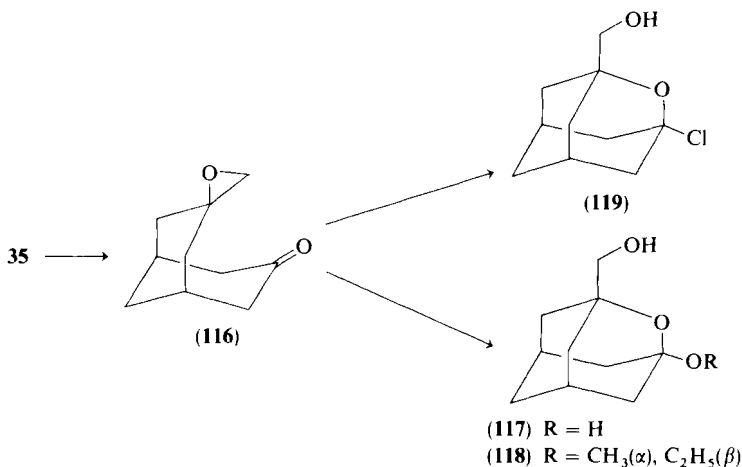
¹⁴¹ H. Stetter and K. Komorowski, *Chem. Ber.* **104**, 75 (1971).

¹⁴² H. Stetter and V. Tillmanns, *Chem. Ber.* **105**, 735 (1972).



derivatives under several conditions. Oxymercuration of **35** with mercury acetate proceeds with participation of the carbonyl group, affording 1-mercury substituted 3-hydroxy-2-oxaadadamantane (**115**), which, after treatment with iodine and then H_2/Ni , yields **112**.¹⁴⁰





Stepanov *et al.*^{143,144} report the ring opening of the monoxide (116) to several 2-oxaadamantane derivatives, where 116 is readily obtained by perbenzoic acid oxidation of 35. Treatment of 116 under various conditions yields different products. Thus, with aqueous acid it yields 1-hydroxy-3-hydroxymethyl-2-oxaadamantane (117), with alcohols (R = CH₃, C₂H₅) in acidic or basic media 1-alkoxy-substituted (118), and with hydrochloric acid 1-chloro-3-hydroxymethyl-2-oxaadamantane (119). 1-Methyl-2-oxaadamantane (120) is prepared by LAH reduction of the carbonyl group in 35 to alcohol 121 and subsequent cyclization with acid.^{140,142}

c. *Dehydration of Alcohols.* Preparation of 2-oxaadamantane derivatives by this method was accomplished first by Stetter's group¹⁴⁵ and seemingly falls into the same category as the conversion of 31 → 110 under catalytic hydrogenation conditions⁵⁸ as already described. This is exemplified by synthesis of 6-methyl-6-dichloromethyl-2-oxaadamantane (124) by LAH reduction of diketone 122 followed by treatment with concentrated sulfuric acid of resultant diol 123. A disadvantage of this reaction is the formation of diene as a by-product; cooperative addition of water to it may compete with the main reaction making the reaction very complex.¹⁴⁶ The same can be said for conversion of bicyclo[3.3.1]nonan-2,7-diol (105a) to 104 with sulfuric acid.¹³⁹ Zefirov and Averina¹⁴⁷ repeated the work of

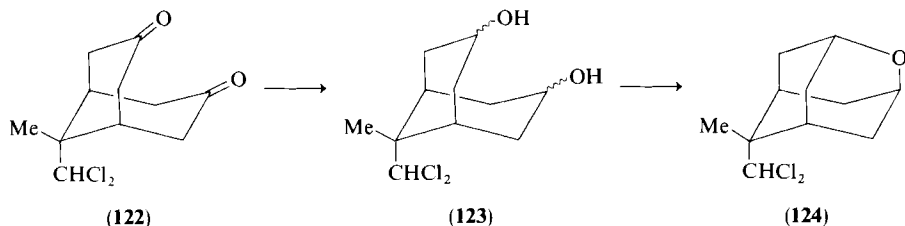
¹⁴³ F. N. Stepanov, T. N. Utochka, and A. G. Yurchenko, *Zh. Org. Khim.* **8**, 1197 (1972).

¹⁴⁴ F. N. Stepanov, T. N. Utochka, A. G. Yurchenko, and S. D. Isaev, *Zh. Org. Khim.* **10**, 1177 (1974).

¹⁴⁵ H. Stetter and J. Mayer, *Chem. Ber.* **92**, 2644 (1959); *Angew. Chem.* **71**, 430 (1959).

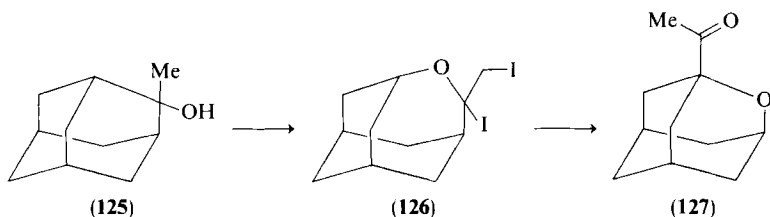
¹⁴⁶ J. P. Schaeffer and L. M. Honig, *J. Org. Chem.* **33**, 2655 (1968).

¹⁴⁷ N. V. Averina and N. S. Zefirov, *J. C. S. Chem. Commun.*, 197 (1973).



Schaefer and Honig¹⁴⁶ and reported it as a novel synthesis of 2-oxaadaman-
tanes, where the treatment of **105a** with concentrated sulfuric acid afforded
104 in 35–40% yields.

d. *Radical Cleavage of 2-Adamantanol*. Oxidation of 2-methyl-2-
hydroxyadamantane (**125**) with lead tetraacetate and iodine affords
ring-enlarged 2-oxahomoadamantane (**126**), which upon treatment with
hydrochloric acid in DMF yields 1-acetyl-2-oxaadamantane (**127**).^{72,148}
Compound **102** is obtained in 50% yield by photochemical oxidation of
106 in the presence of iodine and mercuric oxide,¹⁴⁹ where the “missing”
carbon atom may be eliminated as carbon monoxide. This procedure is sim-
ple, but no mechanism has been established as yet.



e. *Miscellaneous*. Lead tetraacetate oxidation of *endo*-bicyclo [3.3.1]-
nonan-3-ol (**128**) in benzene affords 86% yield of **102**,¹⁵⁰ where **128** is obtained
by sodium reduction of bicyclo[3.3.1]nonan-3-one in absolute ethanol and
the 3-one is prepared by pyrolysis (350°C) of the manganous salt of *cis*-
cyclohexane-1,3-diacetic acid.

7-Methylenebicyclo[3.3.1]non-2-ene (**129**) obtained by pyrolysis of *N,N,N*-
trimethyl-7-methylenebicyclo[3.3.1]nonan-3-ylammonium hydroxide (**130**),
is also a good starting material for **120** which is obtained in 39% yield.¹⁵¹

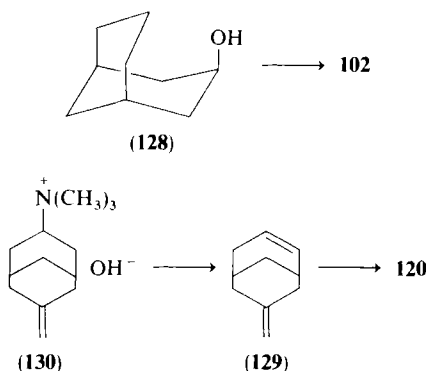
¹⁴⁸ R. M. Black and G. B. Gill, *J. C. S. Chem. Commun.*, 172 (1971).

¹⁴⁹ R. M. Black, G. B. Gill, and D. Hands, *J. C. S. Chem. Commun.*, 311 (1972).

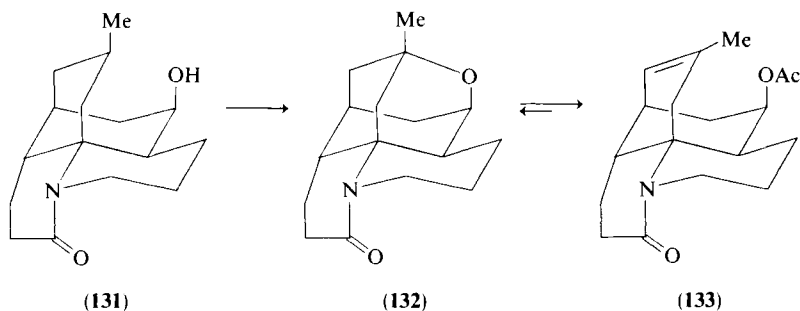
¹⁵⁰ M. Fisch, S. Smallcombe, J. C. Gramain, M. A. McKervery, and J. E. Anderson, *J. Org. Chem.* **35**, 1886 (1970).

¹⁵¹ J. H. Liu, G. A. Gauger, and P. Kovacic, *J. Org. Chem.* **38**, 543 (1973).

Compound **120** is also obtained in 36% yield by diazotization of 7-amino-methylbicyclo[3.3.1]nonan-3-ol with sodium nitrite and acetic acid in aqueous solution at 80–90°C and in 55% yield with isoamyl nitrite in acetic acid at 80–85°C.¹⁵²



Unexpected formation of the oxadamantane skeleton is observed during a series of transformations of the alkaloid lycopoline;¹⁵³ lead tetraacetate oxidation of the alcohol (**131**) gives a 90% yield of the oxadamantane (**132**), which is opened to **133** with boron trifluoride in acetic anhydride and re-cyclized to **132** with aqueous hydrogen bromide.



Lithium aluminum hydride reduction of **31** in the presence of benzylamine affords a 70% yield of 1-benzylamino-2-oxadamantane.¹⁵⁴ This approach is patented as a general method for the preparation of N-substituted 2-oxadamantyl-1-amines.¹⁵⁵ Transannular cyclization of **31** or **35** in the presence

¹⁵² T. A. Wnuk, J. A. Tinnis, M. J. Dolan, S. J. Padejimas, and P. Kovacic, *J. Org. Chem.* **40**, 444 (1975).

¹⁵³ W. A. Ayer, D. A. Law, and K. Piers, *Tetrahedron Lett.*, 2959 (1964).

¹⁵⁴ A. R. Gagneux and R. Meier, *Tetrahedron Lett.*, 1365 (1969).

¹⁵⁵ J. R. Geigy, French Patent 1,500,680 (1967) [*CA* **69**, 96503 (1968)].

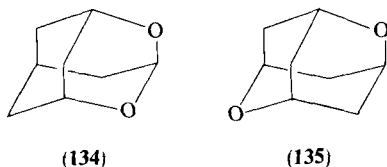
of such nucleophiles as aniline, monomethylaniline, phenol, and thiophenol gives 1-hydroxy-2-oxaadadamantane derivatives.¹⁵⁶ Sodium borohydride reduction of specifically deuterated dione **31** gives deuterated **104**.¹⁵⁷

2. Chemistry and Applications

1-Benzylamino-2-oxaadadamantane hydrochloride has been tested for tuberculostatic activity.¹⁵⁸ 1-(2-Oxa-1-adamantyl)-3-arylsulfonylureas are synthesized for pharmacological testing.¹⁵⁹

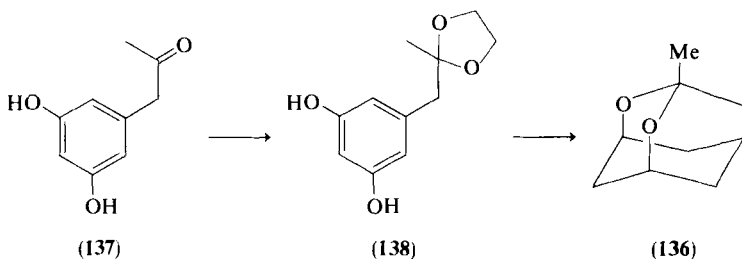
B. DIOXAADAMANTANES

There are two possible dioxaadadamantanes, 2,4- (**134**) and 2,6-dioxaadadamantane (**135**); both are known, but the former only as its derivative.



1. 2,4-Dioxaadadamantanes

a. *Synthesis*. Only one synthesis of 3-methyl-2,4-dioxaadadamantane (**136**) is reported;¹⁶⁰ this starts from 3,5-dihydroxyphenylacetone (**137**).



¹⁵⁶ R. Yamaguchi, K. H. Yang, and M. Kawanishi, *Bull. Chem. Soc. Jpn.* **46**, 673 (1973) [*CA* **78**, 147425 (1973)].

¹⁵⁷ J. Cable and J. K. McLeod, *Aust. J. Chem.* **26**, 2147 (1973).

¹⁵⁸ J. R. Geigy, Ger. Offen. 1,246,722 (1967) [*CA* **67**, 108325 (1967)].

¹⁵⁹ H. Dietrich, South African Patent 6,803,012 (1968) [*CA* **71**, 30363 (1969)].

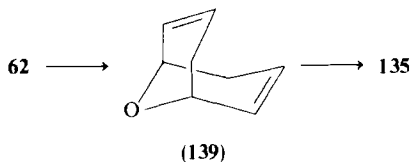
¹⁶⁰ H. Stetter and R. Hess, *Monatsh. Chem.* **98**, 755 (1967).

After protecting the carbonyl group as the ethylene ketal (**138**), the benzene ring is reduced to a cyclohexane ring by catalytic (H_2 , Rh/Pt) hydrogenation. Subsequent treatment with acid yields **136**. However, no attempts for the synthesis of parent compound **134** have been reported.

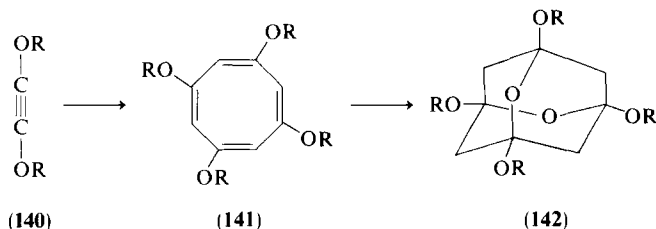
b. *Chemistry and Applications.* Pharmacological data are given for tetrodotoxin, which is a derivative of 2,4-dioxaadamantane.^{161–163}

2. 2,6-Dioxaadamantanes

a. *Synthesis.* Stetter's approach to the 2,6-dioxaadamantane skeleton^{164,165} is characterized by the utilization of double oxymercuration to introduce two oxygen bridges in the skeleton. Similar to the conversion **62** → **63** in the synthesis of the 2,6-diazaadamantane skeleton, readily available **62** is oxymercured with mercury acetate followed by iodine cleavage and dehydrohalogenation, yielding 9-oxabicyclo[3.3.1]nona-2,6-diene (**139**). Repetition of the oxymercuration and iodine cleavage steps leads to diiodo-2,6-dioxaadamantane, from which the halogen is removed by catalytic reduction affording **135** in excellent yield.



Some 1,3,5,7-tetramethoxy-2,6-dioxaadamantane derivatives (**142**, $R = CH_3$) are prepared in a different way; dialkoxyacetylene (**140**) is tetramerized



¹⁶¹ F. Vyskocil, *Pfluegers Arch.* **352**, 155 (1974) [*CA* **82**, 81443 (1975)].

¹⁶² E. Olszewska, L. Janiszewski, and H. Goj, *Bull. Acad. Pol. Sci., Ser. Sci. Biol.* **22**, 523 (1974) [*CA* **82**, 69035 (1975)].

¹⁶³ K. A. Klivington, *Exp. Neurol.* **46**, 78 (1975) [*CA* **82**, 93093 (1975)].

¹⁶⁴ H. Stetter and H.-J. Meissner, *Tetrahedron Lett.*, 4599 (1966).

¹⁶⁵ H. Stetter, H. J. Meissner, and W. D. Last, *Chem. Ber.* **101**, 2889 (1968).

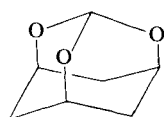
in the presence of ammonia to cyclodeca-1,3,5,7-tetraene (**141**), which is converted to **142** with hydrochloric acid in ethanol.¹⁶⁶ The structure of **142** was determined by X-ray diffraction.¹⁶⁷

Electrophilic halogenation of 9-oxabicyclo[3.3.1]nona-2,6-diene (**139**), a heteroanalog of **39**, in the presence of water and its epoxidation with performic acid results in ring closure to 4,8-disubstituted 2,6-dioxaadamantane derivatives.¹⁶⁸ 4,8-Dibromo-2,6-dioxaadamantane is also prepared from the *syn*-dibromide of 1,5-cyclooctadiene.¹⁶⁹

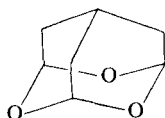
b. *Chemistry and Applications.* No specific accounts are given.

C. TRIOXAADAMANTANES

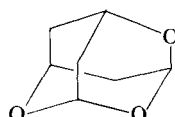
All possible three trioxaadamantane isomers, 2,4,10- (**143**), 2,4,9- (**144**), and 2,4,6-trioxaadamantanes (**145**) are known. However, of the parent molecules only 2,4,10-trioxaadamantane exists.



(143)



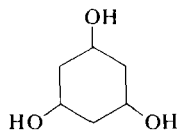
(144)



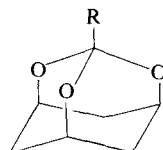
(145)

1. 2,4,10-Trioxaadamantanes

a. *Synthesis.* Stetter's procedure in 1953¹⁷⁰ and in 1954¹⁷¹ is a routine method for the preparation of an orthoformate ester; the reaction of *cis*-phloroglucinol (**146**) with ethyl orthoformate yields 2,4,10-trioxaadamantane



(146)



(147)

¹⁶⁶ J. F. H. Braams, H. J. T. Bos, and F. Arens, *Recl. Trav. Chim. Pays-Bas* **87**, 193 (1968).

¹⁶⁷ J. Kanters and J. B. Hulscher, *Recl. Trav. Chim. Pays-Bas* **87**, 201 (1968).

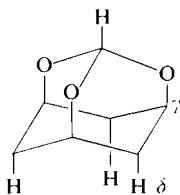
¹⁶⁸ N. V. Averina, N. S. Zefirov, P. P. Kadziauskas, S. V. Pogozina, N. K. Sadovaja, and N. K. Soldatov, *Zh. Org. Chem.* **10**, 1442 (1974).

¹⁶⁹ E. Cuthbertson and D. D. Nicol, *Tetrahedron Lett.*, 2367 (1974).

¹⁷⁰ H. Stetter and K. H. Steinacker, *Chem. Ber.* **86**, 790 (1953).

(**143**) in 75% yield. When $\text{RC}(\text{OEt})_3$ is used, 3-alkyl-substituted adamantanes (**147**) result.

b. *Chemistry and Applications.* From their characteristic structure as orthoformate esters, 2,4,10-oxaadamantanes are expected to be hydrolyzed readily. However, these compounds hydrolyze much more slowly than usual orthoesters and do not react with Grignard or organolithium reagents, probably because of their adamantane-like structures. For this reason, 2,4,10-trioxaadamantane derivatives have found some utilization as protecting groups.¹⁷¹⁻¹⁷³ The PMR spectrum of **143** shows several interesting features¹⁷⁴; long-range coupling is observed, the unique bridgehead hydrogen being coupled to the δ -axial hydrogens with $J = 1.25$ Hz. The role of the oxygens in making visible a coupling that can not be seen in adamantane itself probably reflects an induced significant chemical shift difference between the δ -axial and δ -equatorial hydrogens. Unequal coupling constants are observed for the interaction of the γ -bridgehead hydrogens with the δ -protons, implying that the bridgehead C—H bonds do not have an exactly gauche relationship to the δ - CH_2 s¹⁷⁵ (see **148**). No X-ray data are available to confirm this distortion: microwave data do not preclude it.¹⁷⁶



(**148**)

The cyclization method described in the above synthesis is applied to the preparation of 3-ethoxycarbonylmethyl-2,4,10-trioxaadamantane as a model compound for the synthesis of an antibiotic, Mycomycin.¹⁷⁷ Enthalpies of combustion and sublimation are calculated for **143**.¹⁷⁸

¹⁷¹ H. Stetter and K. H. Steinacker, *Chem. Ber.* **87**, 205 (1954).

¹⁷² J. M. Osbond, P. G. Philpott, and J. C. Wickens, *J. Chem. Soc.*, 2779 (1961).

¹⁷³ F. Bohmann and W. Sucrow, *Chem. Ber.* **97**, 1839 (1964).

¹⁷⁴ E. J. Boros, K. J. Cockran, R. W. King, and J. G. Verkade, *J. Am. Chem. Soc.* **88**, 1140 (1966).

¹⁷⁵ J. G. Verkade, R. W. King, and C. W. Heitsch, *Inorg. Chem.* **3**, 884 (1964).

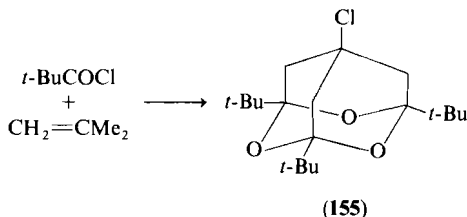
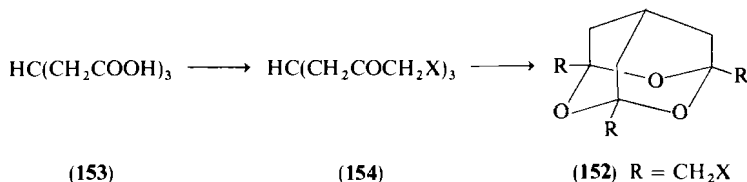
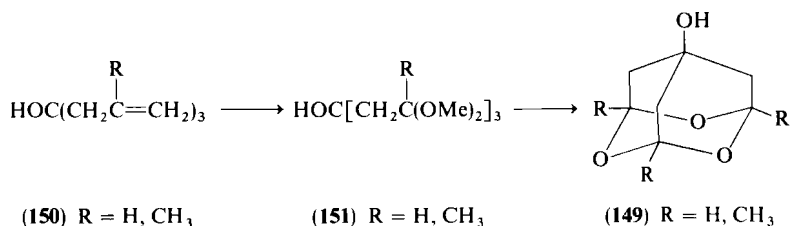
¹⁷⁶ W. D. Slafer and D. O. Harris, *J. Mol. Spectrosc.* **45**, 412 (1973).

¹⁷⁷ F. Bohmann and W. Sucrow, *Chem. Ber.* **97**, 1839 (1964).

¹⁷⁸ M. Mansson, *Acta Chem. Scand., Ser. B* **B28**, 895 (1974) [*CA* **82**, 42850 (1975)].

2. 2,4,9-Trioxaadamantanes

a. *Synthesis.* 7-Hydroxy-2,4,9-trioxaadamantane (**149**, R = H) is prepared by cyclization of triacetylcarbinol (**151**, R = H) with acetic acid, where **151** is obtained from triallylcarbinol (**150**, R = H) by treatment with ozone, then Pd, followed by methanol and calcium chloride. Compound **149** (R = CH₃) is prepared similarly.¹⁷⁹ 1,3,5-Trihalomethyl-2,4,9-oxaadamantane (**152**) is prepared by protonation of methane(tri- α -diazoacetone) (**154**) with either concentrated hydrochloric or hydrobromic acid, where **154** is derived from methanetriacetic acid (**153**) by several steps.¹⁸⁰ One-step synthesis of 7-chloro-1,3,5-tri-*tert*-butyl-2,4,9-trioxaadamantane (**155**) from isobutylene and pivaloyl chloride in the presence of stannic chloride at -15°C is based on the Friedel-Crafts acylation of olefins.¹⁸¹ An intermediate in the cyclization reaction **154** \rightarrow **152** can be isolated.¹⁸²



¹⁷⁹ H. Stetter and M. Dohr, *Chem. Ber.* **86**, 589 (1953).

¹⁸⁰ H. Stetter and H. Stark, *Chem. Ber.* **92**, 732 (1959).

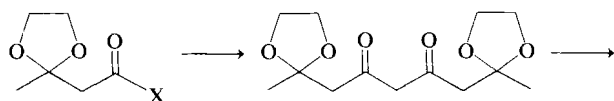
¹⁸¹ E. Herranz and F. Serratosa, *Tetrahedron Lett.*, 4445 (1974).

¹⁸² M. S. Baash and G. G. Krespan, *J. Org. Chem.* **37**, 3378 (1972).

b. *Chemistry and Applications.* Considering that the 2,4,9-trioxadamantane skeleton possesses a symmetrical trioxane moiety, it is expected to undergo ready ring opening. However, no evidence can be found for reversion of any of these derivatives to the carbonyl form; that is, IR shows no carbonyl stretch even at elevated temperatures and these compounds do not react with typical carbonyl reagents. Chlorines in **152** and that at the bridgehead in **155** are surprisingly inert to refluxing alcoholic potassium hydroxide.^{180,181} Such behavior is not unexpected for bridgehead halogens of adamantane derivatives. Clearly the inductive effect of oxygen substantially reduces S_N1 reactivity of the halogen.

3. 2,4,6-Trioxadamantanes

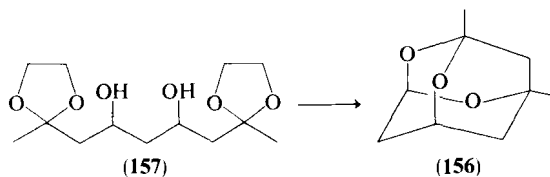
a. *Synthesis.* 1-Methyl-2,4,6-trioxadamantane (**156**) is prepared by cyclization of 2,8-bis(methylenedioxy)nonan-4,6-diol (**157**) with acid, where **157** is obtained by sodium borohydride reduction of the corresponding 4,6-diketone (**158**), which in turn is derived by base-catalyzed condensation of acetylacetone monoethylene ketal (**159**) and methyl acetoacetate ethylene ketal (**160**).¹⁸³ A key step is the last multiple cyclization **157** \rightarrow **156**; the mechanism is uncertain.



(159) X = CH₃

(158)

(160) X = CH₃O

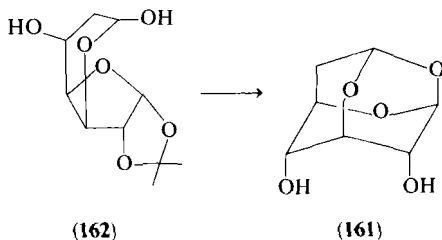


An accidental entry into the 2,4,6-trioxadamantane series was found during a study of the chemistry of 6-deoxy-D-glucohepturonic acid. 8,9-Dihydroxy-2,4,6-trioxadamantane (**161**) is obtained as beautiful crystals by treatment of the lactol (**162**) with aqueous acid.^{184,185}

¹⁸³ H. Stetter and S. Vestner, *Tetrahedron Lett.*, 1681 (1963); *Chem. Ber.* **97**, 169 (1964).

¹⁸⁴ W. Meyer zu Reckendorf, *Angew. Chem., Int. Ed. Engl.* **5**, 665 (1966); *Chem. Ber.* **102**, 2977 (1969).

¹⁸⁵ J. C. Jochims, G. Taigel, and W. Meyer zu Reckendorf, *Tetrahedron Lett.*, 3277 (1967).



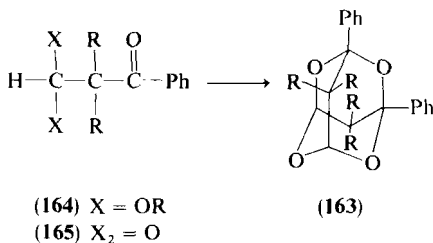
b. *Chemistry and Applications.* Nothing specific is known.

D. POLYOXAADAMANTANES

Among several possible polyoxaadmantanes, only 2,4,6,8-tetraoxaadmantanes are available as their polysubstituted forms.

Synthesis

9,9,10,10-Tetramethyl-1,3-diphenyl-2,4,6,8-tetraoxaadmantane (**163**, $R = CH_3$) is made either by dimerization of an α -formyl ketone, such as α -formyl-isobutyrophenone, (**164**, $R = CH_3$) with sulfuric acid¹⁸⁶ or by dimerization of the aldehyde (**165**) with borontrifluoride etherate.¹⁸⁷ The structure of the product was determined by PMR.¹⁸⁶



Dimerization and condensation of pentane-2,4-dione by molybdenum(VI) oxide tetrachloride ($MoOCl_4$) affords 1,3,5,7-tetramethyl-2,4,6,8-tetraoxaadmantane, the structure of which is determined by elemental analysis, IR, mass, and PMR spectroscopy.¹⁸⁸

¹⁸⁶ L. Dolesj and Z. Arnold, *Collect. Czech. Chem. Commun.* **31**, 4187 (1966).

¹⁸⁷ S.-O. Almqvist, *Acta Chem. Scand.* **22**, 1367 (1968).

¹⁸⁸ M. G. B. Drew, G. W. A. Fowles, D. A. Rice, and K. J. Shanton, *J. C. S. Chem. Commun.*, 614 (1974).

IV. Heteroadamantanes Involving Sulfur

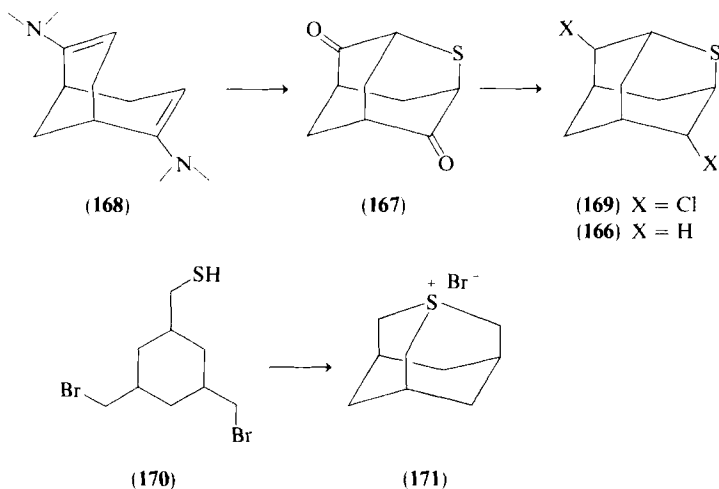
The chemistry of heteroadamantanes involving sulfur has a long history as explained in the introduction.

A. MONOTHIAADAMANTANES

1. Synthesis

Two types of synthesis of this skeleton are reported depending on the positions of the sulfur introduced either at the bridge or at the bridgehead; the former has been studied by Stetter's research group¹⁸⁹⁻¹⁹¹ and the latter by Klages and Schmidt¹⁹² starting from bicyclo[3.3.1]nonane derivatives and cyclohexane derivatives, respectively.

Stetter *et al.* start either from diketone (**45**)^{189,190} or from diene **39**.¹⁹¹ Each of the carbonyls in **45** is protected as the enamine (**168**) and then treated with sulfur dichloride to give 4,8-dicarbonyl-2-thiaadamantane (**167**). The two carbonyl groups in **167** are reduced by Wolff-Kischner reduction to 2-thiaadamantane (**166**), which is also obtained by LAH reduction of 4,8-dichloro-2-thiaadamantane (**169**), prepared in turn from diene **39** and sulfur dichloride.



¹⁸⁹ H. Stetter and H. Held, *Angew. Chem.* **73**, 114 (1961).

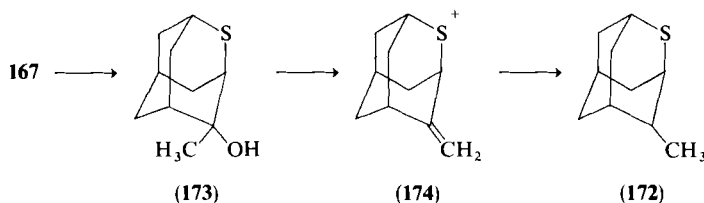
¹⁹⁰ H. Stetter, H. Held, and A. Schulte-Oestrich, *Chem. Ber.* **95**, 1687 (1962).

¹⁹¹ H. Stetter and E. F. Schwartz, *Chem. Ber.* **101**, 2464 (1968).

1-Thiaadamantane as its bromide (**171**) is prepared from the cyclohexane derivative (**170**) and sodium carbonate.¹⁹²

2. Chemistry and Applications

Both **167** and **169** are good starting materials for 4- and 4,8-disubstituted 2-thiaadamantane derivatives, and hydroxyl, alkyl and other several derivatives are derived from them by standard methods.¹⁹²⁻¹⁹⁷ For example, 4-methyl-2-thiaadamantane (**172**) is prepared from **167** by the sequence: (i) methyl Grignard reagent addition to **167** and treatment with hydrazine to give 4-hydroxy-4-methyl-2-thiaadamantane (**173**), (ii) dehydration of **173** to 4-methylene-2-thiaadamantane (**174**), (iii) reduction of **174** with H_2/PtO_2 to **172**.¹⁹⁷



The enthalpy of combustion of **166** is measured as -143.4 ± 0.23 kcal/mol (solid), which leads to an enthalpy of formation as -34.29 ± 0.27 kcal/mol (solid).¹⁹⁸ The base-catalyzed deuterium exchange of the bridgehead hydrogens of **166** and its sulfone were examined; no definite conditions were found under which they would undergo exchange, but the sulfone exchanged rather readily with *i*-PrOK/*i*-PrOD at 100°C leading to a mixture of 1,3-di-D- (34%) and 1-D-derivatives (47%). Similar results were obtained employing potassium carbonate in deuterium oxide as the exchange medium.¹⁹⁹ The data confirm the lack of a steric requirement for sulfone stabilization of carbanions.^{200,201} The bromide ion of **171** can be exchanged for tetraphenylborate or picrate and in the PMR spectrum of **171**, the bridgehead hydrogens

¹⁹² F. Klages and H. Schmidt, *Chem. Ber.* **96**, 2063 (1963).

¹⁹³ S. Landa and J. Janku, *Collect. Czech. Chem. Commun.* **34**, 2014 (1969); **37**, 2269 (1972).

¹⁹⁴ J. Janku, J. Burkhard, and S. Landa, *Z. Chem.* **13**, 103 (1973).

¹⁹⁵ G. Snatzke and B. Wolfram, *Tetrahedron* **28**, 655 (1972).

¹⁹⁶ P. H. Mc. Cabe and W. Routledge, *Tetrahedron Lett.*, 3919 (1973).

¹⁹⁷ J. Janku, J. Burkhard, and L. Vodichka, *Z. Chem.* **15**, 397 (1975).

¹⁹⁸ J. L. Lacina, W. D. Good, and J. P. McCullough, *J. Phys. Chem.* **65**, 1026 (1961).

¹⁹⁹ J. Janku and J. Mitera, *Z. Chem.* **10**, 224 (1970).

²⁰⁰ W. von E. Doering and L. K. Levy, *J. Am. Chem. Soc.* **77**, 509 (1955).

²⁰¹ S. Oae, W. Takagi, and A. Ohno, *J. Am. Chem. Soc.* **83**, 5036 (1961).

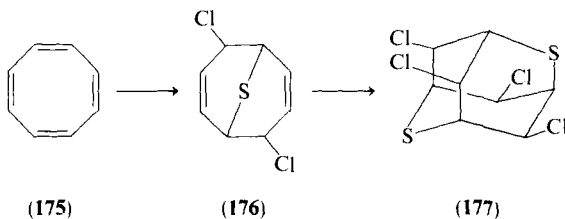
do not show such an unusual deshielding as found in the adamantyl cation.¹⁹² The gas chromatographic characterization of **166** is reported.²⁰²

B. DITHIAADAMANTANES

As in the case of dioxadamantanes, there are two possible dithiadamantanes, 2,4- and 2,6-dithiaadamantanes; both are known as their derivatives, not as parent compounds.

1. 2,6-Dithiaadamantanes

a. *Synthesis.* Addition of sulfur dichloride to cyclo-1,3,5,7-tetraene (**175**) proceeds in two steps yielding 4,8,9,10-tetrachloro-2,6-dithiaadamantane (**177**) via 9-thiabicyclo[3.3.1]nona-4,8-dichloro-2,6-diene (**176**). The approach is similar to the conversion **39** → **169** employed in the synthesis of 2-thiaadamantane (**166**). Structure **177** was determined by PMR analysis,²⁰³ and furthermore, by analysis of its oxidation products²⁰⁴ as described below.



b. *Chemistry and Applications.* Compound **177** when oxidized in acetic acid with hydrogen peroxide gives only one oxidation product, a 2,6-dioxide.²⁰⁴ Formation of this only oxidation product serves as good proof that the original compound has a dithiaadamantane skeleton (symmetry S_4) instead of the isomeric dithiatwistane skeleton (symmetry D_2), which should give two.

2. 2,4-Dithiaadamantanes

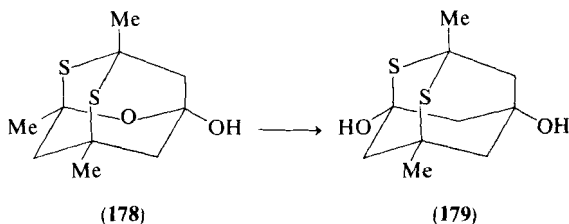
a. *Synthesis.* Treatment of 1,3,5-trimethyl-7-hydroxy-6-oxa-2,4-dithiaadamantane (**178**) with base affords a mixture of several products, from which

²⁰² J. Janku and M. Popl, *J. Chromatogr.* **89**, 319 (1974).

²⁰³ P. Y. Blanc, P. Diehl, H. Fritz, and P. Schlapfer, *Experientia* **23**, 896 (1967).

²⁰⁴ F. Lautenschlager, *J. Org. Chem.* **33**, 2627 (1968).

1,7-dihydroxy-3,5-dimethyl-2,4-dithiaadamantane (**179**) was separated in 20–25% yield by virtue of its high crystallinity. The structure was determined on the basis of its UV and mass spectrum and a complete analysis of its PMR spectrum.²⁰⁵



b. *Chemistry and Applications.* Nothing specific is known.

C. TRITHIAADAMANTANES

They are unknown.

D. TETRATHIAADAMANTANES

Among several possible tetrathiaadamantane isomers, only 2,4,6,8-tetrathiaadamantane derivatives are known and extensively studied.

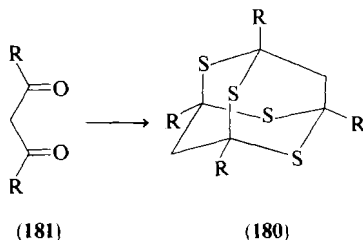
2,4,6,8-Tetrathiaadamantanes

a. *Synthesis.* The first synthesis of the 2,4,6,8-tetrathiaadamantane skeleton was in 1906⁸ as described in the introduction. Pregda's revision of a wrongly assigned structure^{9,10} is depicted there. 1,3,5,7-Tetrasubstituted 2,4,6,8-tetrathiaadamantane (**180**) is prepared from β -diketone **181** either with hydrogen sulfide and hydrogen chloride in ethanol or with thioacetic acid in the presence of zinc chloride.²⁰⁶ However, **180** is not a sole product in both syntheses; several hexathia- and oxathiaadamantane derivatives are co-produced and it is very difficult to separate **180** in a pure state from these complex mixtures. A similar condensation of a β -diketone such as 2-acetyl-1-cyclopentanone with hydrogen sulfide is reported.²⁰⁷

²⁰⁵ S. O. Almquist and K. Olsson, *Chem. Scr.* **1**, 30 (1971).

²⁰⁶ A. Brändström, *Ark. Kemi* **3**, 41 (1951) [*CA* **45**, 7574 (1951)].

²⁰⁷ W. Uhde and K. Hartke, *Arch. Pharm. (Weinheim, Ger.)* **304**, 42 (1971) [*CA* **74**, 141660 (1971)].



b. *Chemistry and Applications.* The PMR spectra of 2,4,6,8-tetrathiaadamantane and its derivatives have been analyzed; long-range coupling is evident as expected and the effect of the heteroatoms upon chemical shifts follows an additive relationship as observed in carbocyclic adamantanes. Detailed interpretation of electron impact fragmentations is given.²⁰⁸ All IR and Raman bands for 1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane are assigned by normal coordinate analysis; the symmetry of the molecules is assumed to be D_{2d} , but the calculated and observed numbers of Raman active vibrations do not correspond well, so that some distortion seems likely. The bending force constants are found to be approximately twice those in a simple cyclic thioether, as expected from the bridged structure of the molecule.^{209,210} The UV spectrum of 1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane has a second maximum absorption at about 270 nm contrary to a single absorption of monocyclic 1,3-dithiane at 250 nm; this is attributed to three-dimensional interaction of the sulfur atoms, which form a 1,3-network.²¹¹ The heat capacity of the same compound is determined as a function of temperature from 5 to 350°K, but no thermal anomaly corresponding to a transition in the crystal structure is observed.²¹² Dianion formation of the compound upon reduction with sodium-potassium alloy results in a development of a bright yellow color (absorption at 430 nm); this color fades upon exposure to air and no ESR signal is observed, excluding the radical-anion. Starting material is recovered upon quenching with various reagents.²¹³ Interesting from both synthetic and mechanistic viewpoints is the report that 3,5-dimethyl-2,4,6,8-tetrathiaadamantane when treated with *n*-butyllithium gives the dianion, which upon treatment with carbon dioxide gives 3,5-dimethyl-2,4,6,8-tetrathiaadamantane-1-carboxylic acid.^{214,215} The

²⁰⁸ K. Olsson and S. O. Almqvist, *Ark. Kemi* **27**, 571 (1967) [*CA* **68**, 87284 (1968)].

²⁰⁹ O. Siimann and J. Fresco, *Spectrochim. Acta, Part A* **27A**, 673 (1971).

²¹⁰ J. E. Barnes, J. A. W. Dalziel, and S. D. Ross, *Spectrochim. Acta, Part A* **27A**, 1247 (1971).

²¹¹ L. K. Dyal and S. Winstein, *Spectrochim. Acta, Part A* **27A**, 1619 (1971).

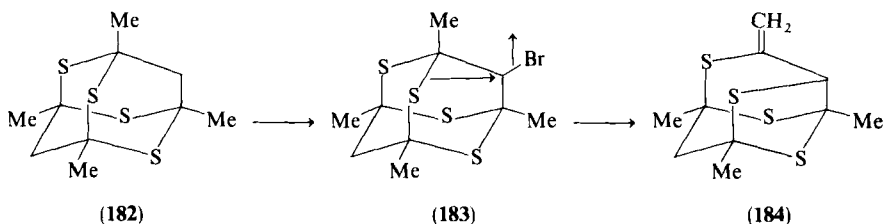
²¹² S.-S. Chang and E. F. Westrum, Jr., *J. Phys. Chem.* **66**, 524 (1962).

²¹³ D. L. Coffen, P. E. Garrett, and D. R. Williams, *J. C. S. Chem. Commun.*, 652 (1968).

²¹⁴ K. Olsson, *Acta Chem. Scand.* **22**, 2390 (1968).

²¹⁵ M. O. Hedblom and K. Olsson, *Ark. Kemi* **32**, 309 (1970) [*CA* **74**, 3591 (1971)].

intermediate dianion was quenched with deuterated water.^{216,217} The solvolysis of 10-bromo-1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane (**183**), readily obtainable by bromination of **182**, shows an effect of neighboring sulfur participation; this bromide has the appropriate trans-antiparallel arrangement of sulfur and the leaving group for participation, yet can be recrystallized unchanged from alcohol. When solvolyzed in refluxing acetic acid, however, it is completely transformed into the rearranged product (**184**).²¹⁸ Similar rearrangement of the bromide with sodium acetate is reported.^{219,220}



X-ray diffraction data are given for **182**.²²¹ 2,4,6,8-Tetrathiaadamantane-thiol was tested for antibacterial and antiviral activity.²²² 1,3,5,7-Tetraalkyl-2,4,6,8-tetrathiaadamantane derivatives are used for lubricant additives.²²³ Poly(methyl methacrylate) with good resistance to heat and air oxidation is prepared by polymerization of the monomer in the presence of **182**.²²⁴

E. PENTATHIAADAMANTANES

There are no reports.

²¹⁶ D. L. Coffen, *Rec. Chem. Prog.* **30**, 275 (1969).

²¹⁷ K. C. Bank and D. L. Coffen, *J. C. S. Chem. Commun.*, 8 (1969).

²¹⁸ D. L. Coffen and W. L. Lee, *J. Org. Chem.* **35**, 2077 (1970).

²¹⁹ B. M. Lerman, G. A. Tolsikov, and Z. Ja. Arefeva, *Izv. Akad. Nauk SSSR, Ser. Chim.* **8**, 1898 (1972) [*CA* **77**, 164639 (1972)].

²²⁰ B. M. Lerman, Z. Ja. Arefeva, L. I. Umanskaja, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Chim.* **11**, 2550 (1974) [*CA* **82**, 57650 (1975)].

²²¹ B. P. Birjukov, B. V. Unkovskii, A. N. Kuznecov, and D. T. Burdelev, *Zh. Strukt. Khim.* **13**, 748 (1972) [*CA* **77**, 169894 (1972)].

²²² British Patent 1,217,207 (1970) [*CA* **74**, 125706 (1971)].

²²³ Ja. M. Slobodin and S. G. Rozenberg, *Khim. Tekhnol. Topl. Masel* **10**, 41 (1965) [*CA* **14**, 9483 (1966)].

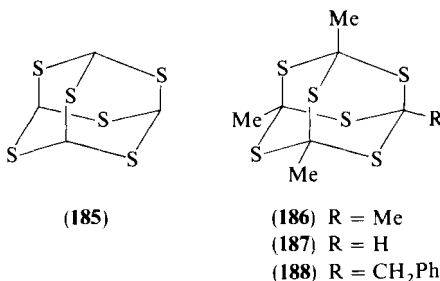
²²⁴ A. Pregda and K. Olsson, *Ark. Kemi* **9**, 163 (1956).

F. HEXATHIAADAMANTANES

The structure has an adamantane skeleton consisting of all six bridge carbons substituted by sulfur atoms. Considering its highly symmetrical structure, it can be assumed to be a quite stable crystalline compound. The history of the preparation of this skeleton is briefly documented in the introduction.⁴⁻⁶

1. *Synthesis*

The parent hexathiaadamantane (**185**) is obtained preparatively when a solution of formic acid and hydrochloric acid in nitrobenzene is allowed to stand for several weeks in a hydrogen sulfide atmosphere; the product which separated is almost insoluble in all common solvents and purification presents a problem. Only large volumes of dimethyl sulfoxide at reflux serve for recrystallization.²²⁴ The reaction of thioacetic acid with formic acid in the presence of zinc chloride gives tetramethyl- (**186**), monomethyl-, dimethyl- and trimethylhexathiaadamantane derivatives (**187**).²²⁵ Other variations include the reaction of thioacetic acid with a β -diketone,²²⁶ and the use of boron trifluoride²²⁷ or aluminum chloride as a catalyst.²²⁸

2. *Chemistry and Applications*

The bridgehead proton of **187** can be substituted by potassium with *t*-BuOK to give a bridgehead anion, which is again substituted with benzyl chloride to give a benzyl compound (**188**).²¹⁴

The PMR spectra of hexathiaadamantane derivatives are not particularly informative.²⁰⁸ The UV spectra reflect the same three-dimensional network

²²⁵ K. Olsson, *Acta Chem. Scand.* **12**, 366 (1958); *Ark. Kemi* **14**, 371 (1959) [*CA* **59**, 14371 (1959)].

²²⁶ K. Olsson, *Ark. Kemi* **28**, 53 (1967) [*CA* **68**, 59548 (1968)].

²²⁷ H. Behringer and G. F. Grunwald, *Justus Liebigs Ann. Chem.* **600**, 23 (1956).

²²⁸ K. Olsson, H. Baeckstrom, and R. Engwall, *Ark. Kemi* **26**, 219 (1967).

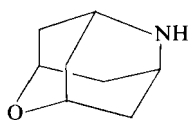
of sulfur–sulfur interaction as in tetrathiaadamantane derivatives.²¹¹ From the site-group analysis of IR and Raman spectra of **185**, it is concluded that the van der Waals forces between molecules in the crystal lattice are strong enough to perturb the symmetry of the individual molecules.²²⁹ The spectra of **186** may be reproduced by normal coordinate analysis, when it is assumed that the compound has T_d symmetry.^{230,231} The strong interaction between individual molecules of **185** is confirmed by X-ray diffraction.²³² No thermal anomalies are found in the heat capacity of **186**.²¹² The crystal and molecular structure of tetrakis(chloromethyl)hexathiaadamantane is reported.²³³ Poly-(methyl methacrylate) with good resistance to heat and air oxidation is prepared by polymerization of the monomer in the presence of about 1 to 2.5% of **186**.²²⁴

V. Heteroadamantanes Involving Two or More Heteroatoms

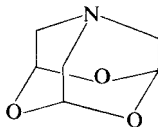
A. AZAOXAADAMANTANES

1. Synthesis

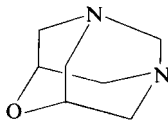
The simplest and most accessible ring system is 2-aza-6-oxaadamantane (**189**), which was constructed by Stetter and Mehren in 1967.²³⁴ However, the oldest is the synthesis of 1-aza-2,4,10-trioxaadamantane (**190**) in 1962²³⁵ followed by those of 1,3-diaza-6-oxaadamantane (**191**)²³⁶ and 1-aza-4,6-dioxaadamantane (**192**) in 1965,²³⁷ all by Stetter and his collaborators. 1-Aza-4,6,10-trioxaadamantane once was called trimorpholine.²³⁸



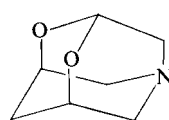
(189)



(190)



(191)



(192)

Stetter's first approach to 3-methyl- (**193**) and 3-phenyl-1-aza-4,6,10-trioxaadamantane (**194**), is based on cyclization of *N,N*-bis(β,β -diethoxy-

²²⁹ H. Spiesecke and R. Mecke, *J. Chem. Phys.* **25**, 577 (1956).

²³⁰ R. Mecke and H. Spiesecke, *Chem. Ber.* **88**, 1997 (1955).

²³¹ J. E. Barnes, J. A. W. Dalziel, and S. D. Ross, *Spectrochim. Acta Part A* **27A**, 1671 (1971).

²³² E. K. Andersen and I. Lindqvist, *Ark. Kemi* **9**, 169 (1956).

²³³ S. Aleby, *Acta Crystallogr., Sect. B* **B30**, 2877 (1974) [*CA* **82**, 50192 (1975)].

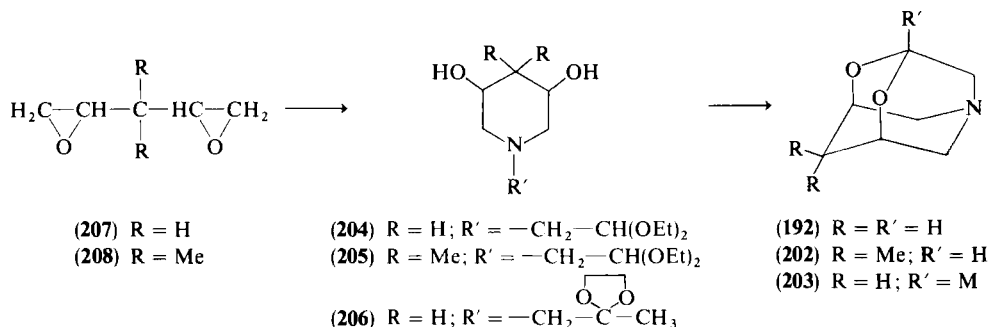
²³⁴ H. Stetter and B. Mehren, *Justus Liebigs Ann. Chem.* **709**, 170 (1967).

²³⁵ H. Stetter and H. Stark, *Chem. Ber.* **95**, 574 (1962).

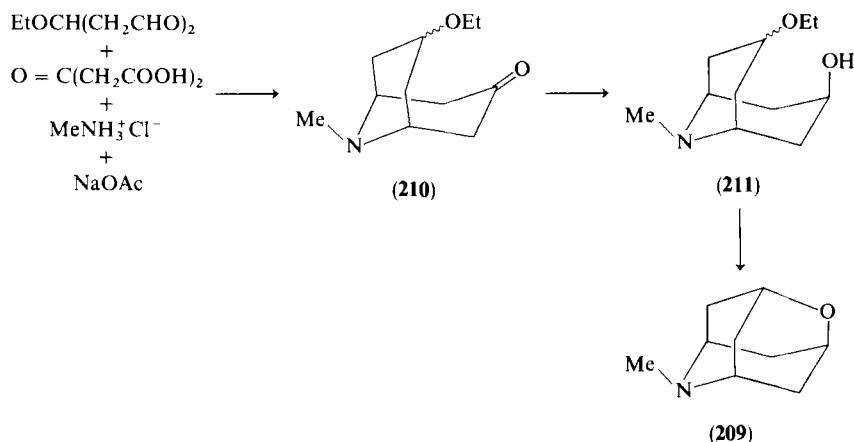
²³⁶ H. Stetter and H.-J. Meissner, *Chem. Ber.* **96**, 2827 (1963).

²³⁷ H. Stetter and K. Zoller, *Chem. Ber.* **98**, 1446 (1965).

²³⁸ L. Wolff and R. Marburg, *Justus Liebigs Ann., Chem.* **363**, 169 (1908).



Most extensively studied is the synthesis of the 2-aza-6-oxa-adamantane ring system. The original preparation is that of 2-methyl-2-aza-6-oxaadamantane (**209**), which starts from the Mannich condensation of acetonediacetic acid, β -ethoxyglutaraldehyde, and methylamine to yield *N*-methyl-9-azabicyclo[3.3.1]nonan-3-ethoxy-7-one (**210**), which is reduced (H_2/Ni) to alcohol **211**. Treatment of **211** with hydrobromic acid affords **209**.²³⁴ Some disadvantages of this procedure are that the product is not parent compound **189**, but its *N*-methyl derivative (**209**) and that the route to **211** is troublesome, laborious and gives poor yields. Improved routes were devised by Ganter and Portmann;²³⁹ and then by Stetter and Heckel¹¹⁴ both starting from cyclooctadiene (**62**).

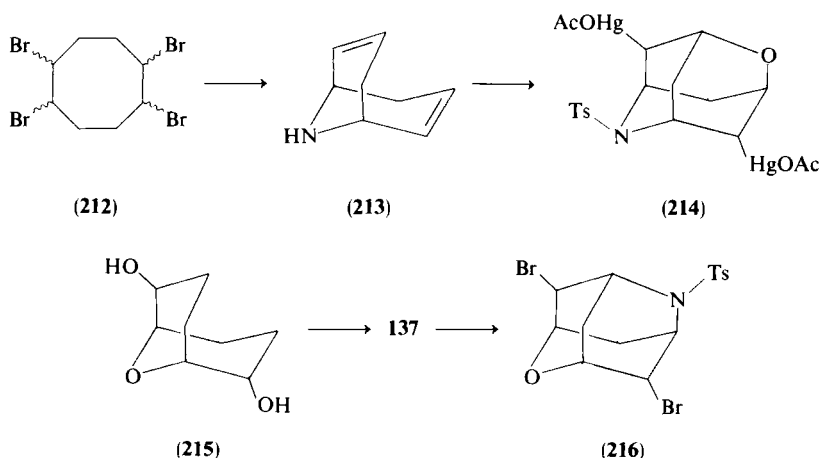


The significant difference is that in the final cyclization step from the bicyclo to the tricyclo system the oxygen bridge is formed in the former and the nitrogen bridge in the latter procedure. Thus, the first step in the former

²³⁹ C. Ganter and R. E. Portmann, *Chimia* **25**, 246 (1971).

is the construction of the 9-azabicyclo[3.3.1]nonane part: **62** is brominated to give the tetrabromide (**212**), which is heated with ammonia to yield 9-azabicyclo[3.3.1]nona-2,6-diene (**213**). The amino group in **213** is tosylated and cyclized by oxymercuration to a 1-aza-6-oxaadamantane derivative (**214**), reduction of which leads to **189**.¹¹⁴ A process **62** → **212** → **213** → **64** is comparable to **62** → **63** → **64** for the synthesis of the 2,6-diazaadamantane skeleton.^{59,60} Oxygen bridge formation in the cyclization of **64** to **214** is similar to the conversion of **39** → **107** employed for the synthesis of the 2-oxaadamantane skeleton.^{134,136}

In the latter approach, **62** is converted to 2,6-dihydroxy-9-oxabicyclo[3.3.1]nonane (**215**), hydration of which with hydrogen bromide and then with trialkylamine affords **139**. This process is comparable to **62** → **139** for the synthesis of the 2,6-dioxaadamantane system.^{164,165} Compound **139** is treated with *N,N*-dibromo-*p*-toluenesulfonamide to give 2-tosyl-4,8-dibromo-2-aza-6-oxaadamantane (**216**), reduction of which gives rise to **189**. This is similar to the **64** → **65** → **66** → **47** conversion used for the synthesis of the 2,6-diazaadamantane ring system.^{59,60} Another approach different from the **64** to **214** route employed by Stetter and Heckel¹¹⁴ was devised by Portmann and Ganter,²⁴⁰ who treated **64** with NBS in acidic medium affording *N*-tosylated 2,6-dibromo-2-aza-6-oxaadamantane.

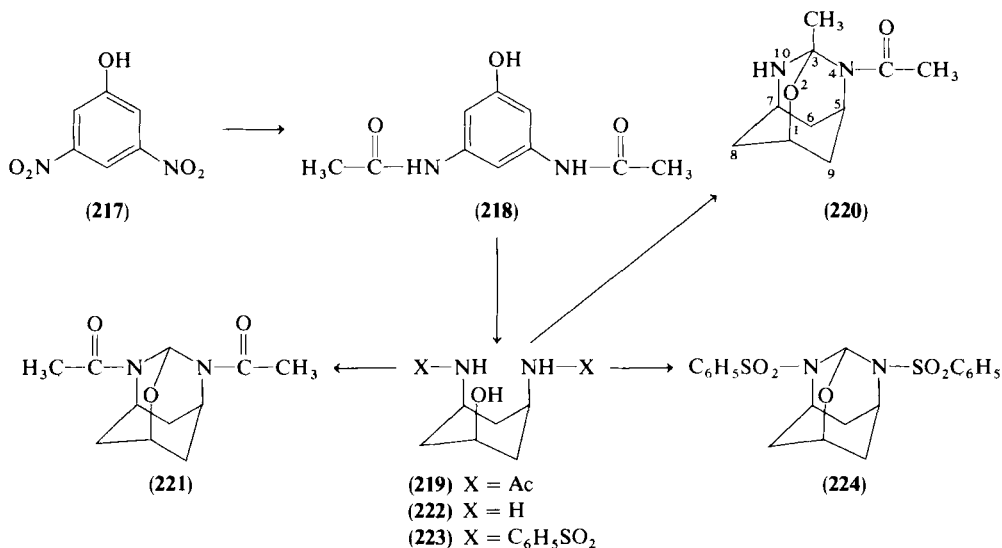


Recently a new ring system, 2-oxa-4,10-diazaadamantane, was prepared as its derivatives from 2,4-dinitrophenol (**217**).²⁴¹ 2,4-Diacetylaminophenol (**218**) is reduced to the cyclohexane derivative (**219**), which is cyclized either

²⁴⁰ R. E. Portmann and C. Ganter, *Helv. Chim. Acta* **56**, 1962 (1973).

²⁴¹ H. Stetter and G. J. Steffens, *Chem. Ber.* **105**, 1755 (1972).

to 3-methyl-4-acetyl-2-oxa-4,10-diazaadamantane (**220**) or to 4,10-diacetyl-2-oxa-4,10-diazaadamantane (**221**). 4,10-Dibenzenesulfonyl derivative **224** is also prepared by cyclization of the corresponding cyclohexane derivative **223**, which is derived from **219** via **222**.



2. Chemistry and Applications

The 1,3-diaza-6-oxa- and 2-oxa-4,10-diazaadamantane rings are similar to the 1,3-diazaadamantane ring which has a common N—C—N linkage in the skeleton. They all are unstable to aqueous mineral acids. Thus, the ring opening of **191** with nitric acid and benzoyl chloride affords *N,N'*-dinitro- (**225**) and *N,N'*-dibenzoyl-9-oxabispidine (**226**), respectively,²³⁶ and hydrolysis of **221** gives **222**.²⁴¹ By contrast, the 1-aza-4,6-dioxaadamantane ring system is stable to aqueous mineral acid.²³⁷

The relative and absolute configurations of diepoxydicarbazoles involving the 2,6-dioxa-4,8-diazaadamantane system were determined in the course of a study on indole and indole alkaloids.²⁴² Water-soluble azo, anthraquinone, and phthalocyanine dyes which are substituted by a 4-chloro-*s*-triazin-2-ylamino group can be quaternized with a 1-aza-3-methyl-4,6,10-trioxaadamantane unit in aqueous medium at 40–50°C.²⁴³ Dyes mixed with

²⁴² H. Fritz and R. Oehl, *Justus Liebigs Ann. Chem.* **10**, 1628 (1973).

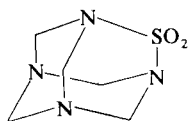
²⁴³ G. A. Gamlen, C. Morris, D. F. Scott, and H. J. Twitchett, British Patent 999,233 (1965) [*CA* **64**, 14319 (1966)].

1-aza-4,6,10-trioxaadamantane show deep shades of color with excellent fastness to light in cellulosic fibers.²⁴⁴

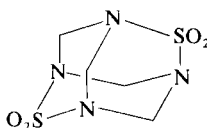
B. AZATHIAADAMANTANES

1. Synthesis

Among possible azathiaadamantane isomers, 1,3,5,7-tetraaza-2-thiaadamantane 2,2-dioxide (**225**)²⁴⁵ and 1,3,5,7-tetraaza-2,6-dithiaadamantane 2,2,6,6-tetraoxide (**226**)²⁴⁶ have been known for a long time.



(225)



(226)

Paquin in 1948 found that a strongly exothermic reaction occurred when 40% formaldehyde was added to a solution of sulfamide in 25% aqueous ammonia. At once beautiful crystals precipitated; they were recrystallized from 96% alcohol to give a compound, $C_5H_{10}N_4SO_2$, mp 224–225°C, in 88% yield.²⁴⁵ From the similar character to hexamethylenetetramine, he named this product “pentamethylenetetramine sulfone”; it is **225**. One year later, in 1949, Hecht and Henecka at Bayer research laboratory reported that a condensation product from one mole of sulfamide in strong mineral acid and two moles of formaldehyde showed very strong toxicity and was five times more toxic than strychnine. They called this product (**226**) “tetramethylenedisulfotetramine.”²⁴⁶

Craig and co-workers²⁴⁷ reported the synthesis of 1-aza-2,4,10-trithiaadamantane (**227**) as a by-product in the reaction of ammonium dithiocarbamate with an aqueous solution of chloroacetaldehyde. The same compound is reported to be obtained by the reaction of mercaptoacetaldehyde with ammonia²⁴⁸ and then by the reaction of tri(2,2-bis(ethoxy)ethyl)amine (**228**) with hydrogen sulfide in the presence of hydrobromic acid.²⁴⁹ The

²⁴⁴ G. A. Gamlen, C. Morris, D. F. Scott, and H. Twitchett, British Patent 1,012,823 (1965) [*CA* **68**, 115637 (1968)].

²⁴⁵ A. M. Paquin, *Angew. Chem.* **60**, 316 (1948).

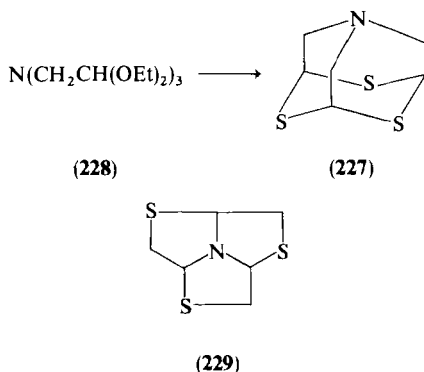
²⁴⁶ G. Hecht and H. Henecka, *Angew. Chem.* **61**, 365 (1949).

²⁴⁷ D. Craig, J. J. Shipman, A. Hawthorne, and R. Fowler, *J. Am. Chem. Soc.* **77**, 1283 (1955).

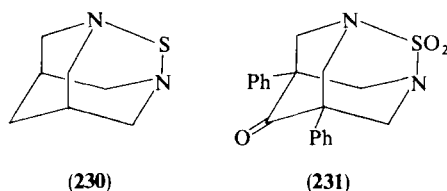
²⁴⁸ M. Thiel, F. Asinger, and K. Schmiedel, *Justus Liebigs Ann. Chem.* **611**, 121 (1958).

²⁴⁹ M. Thiel, F. Asinger, K. Schmiedel, H. Petschik, R. Haberl, and O. Hromatka, *Monatsh. Chem.* **91**, 437 (1960).

product in the last two reactions is the same, but different from that of Craig's. After several investigations, the product in Craig's experiment was finally corrected as hexahydro-1,3,5-triaza-6*b*-azacyclopenta[*c,d*]pentalene (229).²⁵⁰



1,3-Diaza-2-thiaadamantane (230) can be obtained by the reaction of bispidine (51) with diethyl thiocarbonate^{251,252} or from 1,3-diazaadamantan-6-one (61, R = C₆H₅) upon treatment with sulfonyl chloride;²⁵³ in the latter case the product is 3,7-diphenyl-1,3-diazaadamantan-6-one 2,2-dioxide (231).



Isomeric 1,3-diaza-6-thiaadamantane 6,6-dioxide (232) is prepared by cyclocondensation of 3-benzenesulfonyl-9-thia-3,7-diazabicyclo[3.3.1]nonane-9,9-dioxide (233) with formaldehyde, where 233 is derived from *N*-benzenesulfonyl-2,6-dimethylthiomorpholine (234).²⁵⁴

An entry to 2-aza-6-thiaadamantane (235) from *N*-tosyl-9-azabicyclo[3.3.1]nona-2,6-diene (64) and sulfur dichloride is similar to that of 2,6-diazaadamantane, where *N,N*-dibromo-*p*-toluenesulfonamide is used in-

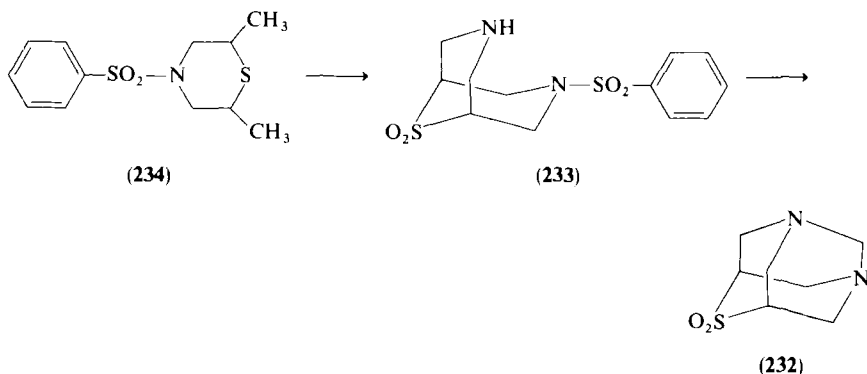
²⁵⁰ R. C. Fort, Jr. and W. L. Semon, *J. Org. Chem.* **32**, 3685 (1967).

²⁵¹ F. Ramirez, J. Marecek, I. Ugi, and D. Marquarding, *Phosphorus* **8**, 91 (1973) [*CA* **80**, 107558 (1974)].

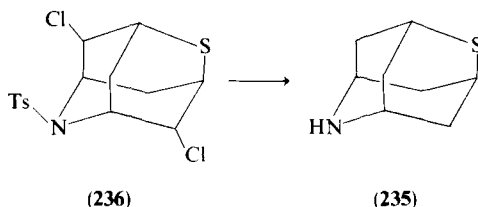
²⁵² P. Andersen and K. E. Hjortaa, *Acta Chem. Scand.* **14**, 829 (1960).

²⁵³ H. Stetter and R. Merten, *Chem. Ber.* **90**, 868 (1957).

²⁵⁴ H. Stetter and J. Schoeps, *Chem. Ber.* **103**, 205 (1970).



stead of sulfur dichloride.^{59,60,114} This procedure was adopted by Stetter and Heckel¹¹⁴ and by Ganter and Portmann.^{239,255}



2. Chemistry and Applications

Compound **225** can be recrystallized from a large volume of water but gradually decomposes into starting materials, especially in the presence of aqueous mineral acids in a process similar to that for hexamethylenetetramine. When treated with concentrated nitric acid, it yields hexogen (cyclotrimethylenetrinitroamine, an explosive).²⁴⁵ Similar properties can be expected for **226**, which is characterized by its high toxicity.²⁴⁶

1,3-Diaza-2-thiaadamantane (**230**) and its 2,2-dioxide (**231**) are known to be opened to bispidine derivatives when subjected to the action of alkylating agents such as phosgene or *p*-toluenesulfonyl chloride.²⁵⁶ The halogens of **236** are known to undergo readily S_N2 displacement, for example, with sodium iodide in acetone. Compared to bimolecular attack on the bridge positions of adamantane itself, the ease of these reactions may be a consequence of the replacement of one of the 1,3-diaxial hydrogens by a heteroatom, or it may involve some sort of electronic stabilization of the transition state.²⁵³

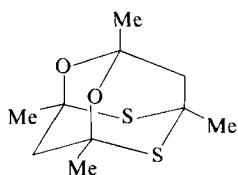
²⁵⁵ C. Ganter and R. E. Portmann, *Helv. Chim. Acta* **54**, 2069 (1971).

²⁵⁶ D. Misiti and S. Chiavarelli, *Gazz. Chim. Ital.* **96**, 1696 (1966).

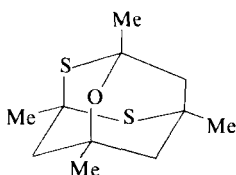
C. OXATHIAADAMANTANES

Synthesis

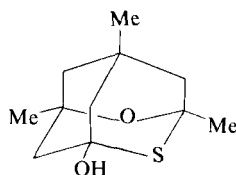
Formation of various oxathiaadamantane derivatives such as tetramethyl-substituted dioxadithia- (**237**), monooxadithia- (**238**), and monooxamono-thiaadamantane (**239**) is observed among many products in the reaction of 2,4-pentadione with hydrogen sulfide.^{257,258}



(237)

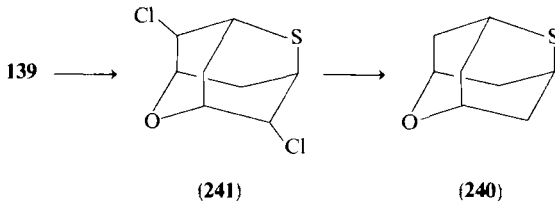


(238)



(239)

An entry to 2-oxa-6-thiaadamantane (**240**) from 9-oxabicyclo[3.3.1]nona-2,6-diene (**139**) using sulfur dichloride by Stetter *et al.*²⁵⁹ and by Ganter and Wicker²⁶⁰ is a so-called routine procedure via 4,8-dichloro-2-oxa-6-thiaadamantane (**241**).



²⁵⁷ K. Olsson, *Ark. Kemi* **26**, 465 (1967).

²⁵⁸ J. Hedman, P. Heden, R. Nordberg, C. Nordling, and B. J. Lindberg, *Spectrochim. Acta Part A* **26A**, 761 (1970).

²⁵⁹ H. Stetter, H.-J. Weissner, and W.-D. Last, *Chem. Ber.* **101**, 2889 (1968).

²⁶⁰ C. Ganter and K. Wicker, *Helv. Chim. Acta* **51**, 1599 (1968).

Selenophenes

ANNA-BRITTA HÖRNFELDT

*Department of Organic Chemistry 1, Chemical Center,
University of Lund, Lund, Sweden*

| | |
|--|-----|
| I. Introduction | 127 |
| II. Theoretical Treatment | 128 |
| III. Dipole Moments | 129 |
| IV. Determination of Geometry and Conformations | 129 |
| V. Spectroscopic Studies | 131 |
| A. IR, UV, and Microwave Spectra | 131 |
| B. Mass Spectra | 132 |
| C. NMR Spectroscopic Studies | 133 |
| D. Electron Spectroscopy for Chemical Analysis | 136 |
| VI. Preparation of Selenophenes | 136 |
| A. From Acyclic Compounds | 136 |
| B. From Other Ring Systems | 140 |
| VII. Electrophilic and Nucleophilic Substitution Reactions | 141 |
| A. Comparative Studies | 141 |
| B. Inverted Reactivity of Aryllithium Derivatives | 144 |
| VIII. Reactions via Organometallic Intermediates | 145 |
| A. Metalation and Halogen-Metal Exchange | 145 |
| B. Ring-Opening Reactions | 145 |
| IX. Carbonyl-Substituted Derivatives of Selenophene | 149 |
| A. Preparation and Reactions of Formylselenophenes | 149 |
| B. Conformations of 2-Formyl- and 2-Acetylselenophenes | 152 |
| X. Hydroxyselenophenes and Their Sulfur and Selenium Analogs | 155 |
| A. Preparation and Tautomeric Properties | 155 |
| B. Reactions | 157 |
| XI. Selenophenes with Nitrogen-Containing Substituents | 158 |
| A. Cyano Derivatives and Their Reactions | 158 |
| B. Amino Derivatives and Their Reactions | 160 |
| C. Meisenheimer Complexes in the Selenophene Series | 163 |
| D. Pharmacologically Interesting Selenophenes | 163 |
| XII. Selenophenes of Potential Technical Utility | 164 |
| XIII. Miscellaneous | 166 |

I. Introduction

Although the first selenophene derivative, 2,5-dimethylselenophene, has been known for almost 100 years, the real development of selenophene

chemistry began with the investigations of Yur'ev and co-workers. Their results and other contributions to selenophene chemistry up to 1970 have been reviewed by Magdesieva.¹ Another review, by Magdesieva and Zefirov,² covering the literature from the same period compares selenophene with its isologs, thiophene and furan. A shorter review of the same period is given by Livingstone in Rodd's "Chemistry of Carbon Compounds."³ A continuous retrieval of information from the literature is made by Gronowitz⁴ in his reviews of thiophenes and their selenium and tellurium analogs. This chapter reviews developments in selenophene chemistry over the last decade.

II. Theoretical Treatment

Nonempirical calculations on the electronic structure of molecules containing third-row elements have been largely concerned with linear molecules. However, selenophene has been the subject of a study using an STO-3G basis set.⁵ Addition of five 4*d*-orbitals improves the total energy by an amount only slightly greater than the improvement caused by the addition of the single 4*s* function, strongly suggesting that the 4*d*-orbitals are assuming the role of polarization functions. They are increasing the variational flexibility of the system rather than making a significant contribution to the ground state bonding. The calculated parameters are in good agreement with the experimental geometry, as determined by microwave spectroscopy.

The electronic structures of furan, thiophene, and selenophene, their protonated complexes, and their anions have been calculated by the extended Hückel method.⁶ The results of these calculations have been used to determine the influence of the heteroatom on the degree of aromaticity and electron density.

In a study of quantum chemical calculations of reactivity, it was found that charge densities give only qualitative agreement with experimental reactivities in electrophilic substitution, whereas semiquantitative agreement is obtained with the localization energies.⁷

¹ N. N. Magdesieva, *Adv. Heterocycl. Chem.* **12**, 1 (1970).

² N. N. Magdesieva and N. S. Zefirov, in "Organic Selenium Compounds: Their Chemistry and Biology" (D. L. Klayman and W. H. H. Günther, eds.), Chapter XI, p. 427. Wiley (Interscience) New York, 1973.

³ R. Livingstone, in "Rodd's Chemistry of Carbon Compounds" (S. Coffey, ed.), 2nd ed., Chapter 3, p. 313. Elsevier, Amsterdam, 1973.

⁴ S. Gronowitz, *Org. Comp. Sulphur, Selenium, Tellurium* **5**, 247 (1979).

⁵ R. H. Findlay, *J. C. S., Faraday II* **70**, 1397 (1974).

⁶ A. A. Karel'ov, G. A. Chmutova, M. B. Zuev, and E. G. Kataev, *Zh. Fiz. Khim.* **50**, 566 (1976).

⁷ I. A. Abronin, V. P. Litvinov, G. M. Zhidomirov, A. Z. Dzhumanazarova, and Ya. L. Gold'farb, *Khim. Geterotsikl. Soedin.*, 199 (1980).

III. Dipole Moments

Five-membered heteroaromatic compounds containing group VIA elements, such as oxygen, sulfur, selenium, and tellurium, constitute an excellent series for investigating the influence of the heteroatom on molecular electronic properties. The dipole moments of selenophene and some simple halogeno-, cyano-, and formylselenophenes have been measured and the conformations of these compounds discussed.⁸ The numerical values and the direction of the dipole moments of these four congener compounds and their corresponding tetrahydro derivatives are very useful parameters in structure–reactivity correlation studies. The dipole moments of the eight compounds studied have the negative end of the dipole on the heteroatom.⁹ The aromatic heterocycles exhibit dipole moments that are much lower than those for the saturated ones. This difference can be used as a measure of the mesomeric moment of the unsaturated compound and as a good criterion for establishing the ground-state aromaticity order of the heterocycles, in the sense that the greater the mesomeric moment, the more aromatic is the five-membered heterocycle.¹⁰

From a study of the microwave spectrum of 2-methylselenophene, the second-order Stark effect in the ground state was determined.¹¹ The technique used was double radiofrequency–microwave resonance. For the identification by the double resonance method transitions of chiefly the A-state were chosen. From these observations the components of the dipole moment of 2-methylselenophene and the total dipole moment were determined.

IV. Determination of Geometry and Conformations

NMR using liquid crystal solvents is now a well-established tool for the investigation of molecular structure. Selenophene was studied in a liquid crystal composed of sodium sulfate, decanol, deuterium oxide, and sodium decylsulfate.¹² The refined direct couplings were obtained iteratively with the help of a computer. The ratios of the interproton distances were calculated from the direct couplings and found to be in good agreement with corresponding values calculated from the microwave data.

⁸ H. Lumbroso, D. Mazet, J. Morel, and C. Paulimier, *C. R. Acad. Sci., Ser. C* **271**, 1481 (1970).

⁹ F. Fringuelli, S. Gronowitz, A.-B. Hörnfeldt, and A. Taticchi, *J. Heterocycl. Chem.* **11**, 827 (1974).

¹⁰ H. Lumbroso, D. M. Bertin, F. Fringuelli, and A. Taticchi, *J. C. S. Perkin II*, 775 (1977).

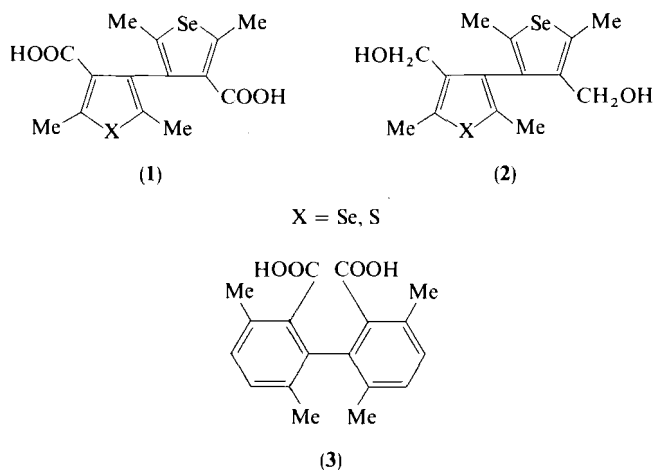
¹¹ N. M. Pozdeev, L. N. Gunderova, R. G. Latypova, and N. N. Magdesieva, *Zh. Strukt. Khim.* **19**, 747 (1978).

¹² K.-I. Dahlqvist and A.-B. Hörnfeldt, *Chem. Scr.* **1**, 125 (1971).

When a molecule exhibits large internal motions difficulties arise in using most available techniques for the determination of molecular geometry. In a study of 2,2'-biselenophene it was shown that although internal motion is present, useful structural information can still be obtained in the liquid crystal phase and that, at present, other techniques are not available for obtaining equivalent information, at least not in a liquid-like phase.¹³ This study also demonstrates the usefulness of the heteroatom satellites, and in particular of Se—H dipolar couplings.

Fringuelli and Taticchi¹⁴ found good linear correlations between the coupling constant J_{23} and the single C—C—H angles of furan, thiophene, selenophene, and pyrrole. The XC(2) bond lengths of these heterocycles are linearly correlated with the single-bond covalent radii of the heteroatoms.

CD and ORD measurements are a useful tool in studying configuration and conformation. The configuration of optically active 4,4'-dicarboxy-2,2',5,5'-tetramethyl-3,3'-biselenienyl (**1**, X = Se) relative to its thiophene analog (**1**, X = S), was determined by reducing both to the corresponding 4,4'-dihydroxymethyl derivatives (**2**), which could be related to each other by the quasi-racemate method and by circular dichroism studies.¹⁵ Compounds **1** have also been related to 3,3',6,6'-tetramethyl-2,2'-diphenic acid (**3**), and it was found that the levorotatory form of **1** (X = Se, S) and the dextrorotatory form of **3** have the *R*-configuration.¹⁶



¹³ G. Chidichimo, F. Lelj, M. Longeri, N. Russo, and C. A. Veracini, *Chem. Phys. Lett.* **67**, 384 (1979).

¹⁴ F. Fringuelli and A. Taticchi, *Gazz. Chim. Ital.* **103**, 453 (1973).

¹⁵ S. Gronowitz and T. Frejd, *Acta Chem. Scand.* **26**, 2279 (1972).

¹⁶ R. Håkansson, S. Gronowitz, J. Skramstad, and T. Frejd, *Chem. Scr.* **7**, 131 (1975).

In order to understand the rates of racemization of biphenyls and biheterocyclics, an accurate knowledge of their geometric structure is essential. Such knowledge makes it possible to estimate the amount of interference caused by substituents in the vicinity of the pivot bond in an assumed coplanar transition state for rotation. A study of the crystal structure of **1** ($X = Se$) found that the selenophene rings have a small but significant deviation from planarity and are nearly perpendicular to each other.¹⁷ The deviation from 90° is such that the carboxyl groups are in transoid positions.

Magnetic circular dichroism (MCD) has now become a tool with valuable applications to analytical and structural studies. The MCD spectrum of thiophene is only slightly perturbed by substituents, and this is also expected to be true of the quite similar MCD spectra of selenophene.¹⁸ These molecules can therefore be classified as "hard" chromophores.

V. Spectroscopic Studies

A. IR, UV, AND MICROWAVE SPECTRA

There is a continual interest in the UV spectra of chalcone analogs of type **4**, where R may be the selenienyl moiety.¹⁹ The IR spectra of these compounds have also been measured in the solid state and in solutions of carbon tetrachloride and chloroform.²⁰ The interaction between the ring and the



(4)

substituents in selenophene has been examined by studying the integrated intensities of IR ring-stretching bands.²¹ Direct interactions between the selenium and the substituent almost certainly exist but do not seem generally important.

Charge-transfer complexes between heteroaromatic five-membered ring compounds and tetracyanoethylene have been studied in solution at $20^\circ C$.²² Spectra, stability constants, and empirical calculations of ionization energies

¹⁷ B. Aurivillius, *Chem. Scr.* **1**, 25 (1971).

¹⁸ B. Nordén, R. Håkansson, P. B. Pedersen, and E. W. Thulstrup, *Chem. Phys.* **33**, 355 (1978).

¹⁹ S. V. Tsukerman, V. D. Orlov, and V. F. Lavrushin, *Khim. Geterotsikl. Soedin.*, **Sb. 5**, 67 (1969).

²⁰ S. V. Tsukerman, V. D. Orlov, Yu. S. Rozum, and V. F. Lavrushin, *Khim. Geterotsikl. Soedin.*, **Sb. 5**, 623 (1969).

²¹ G. P. Ford, T. B. Grindley, A. R. Katritzky, M. Shome, J. Morel, C. Paulmier, and R. D. Topsom, *J. Mol. Struct.* **27**, 195 (1975).

²² G. G. Aloisi, S. Santini, and G. Savelli, *J. C. S., Faraday I* **71**, 2045 (1975).

confirm the $\pi \rightarrow \pi^*$ nature of these complexes and that the inner orbitals of the donors are involved in the charge-transfer interaction.

The photoelectron spectrum of selenophene vapor down to 1350 Å has been studied. By analogy with the other heterocyclic derivatives, Rydberg-type transitions occur, leading to the first ionization potential of the molecule.²³

The main difference between thiophene and selenophene is that on flash photolysis in the former SH and not S₂, while in the later Se₂ and not SeH were detected in the photodecomposition products. This suggests that in selenophene the dissociation takes place at the Se site and that Se₂ is formed as a result of the recombination of the Se atoms.²⁴

Vertical ionization energies of the two highest molecular orbitals and of orbitals mainly localized on the substituent of α -substituted derivatives of furans, thiophenes, selenophenes, and tellurophenes have been determined.²⁵ Assignments of some of the bands other than the first two in the photoelectron spectra of tellurophene and selenophene are proposed, and the effect of the ring on the orbitals mainly localized on the substituent is briefly discussed.

Data from microwave spectra on the centrifugal effect of rotational transitions of selenophene and its deuterium-substituted derivatives have been determined experimentally and compared with the calculated theoretical values of the centrifugal stretching constants by means of the force constants determined from the solution of the inverse vibrational problem.²⁶ The two sets of values show good agreement, indicating that the system of force constants obtained for selenophene correctly reflects the characteristic features of the force field of the molecule.

B. MASS SPECTRA

The mass spectrum of selenophene has been recorded and the fragmentation pattern compared with those of the other congener heteroaromatic compounds.²⁷ The analogous fragments observed for the four heterocycles are given in Scheme 1.

Selenophene and tellurophene have an additional fragmentation as shown in Scheme 2.

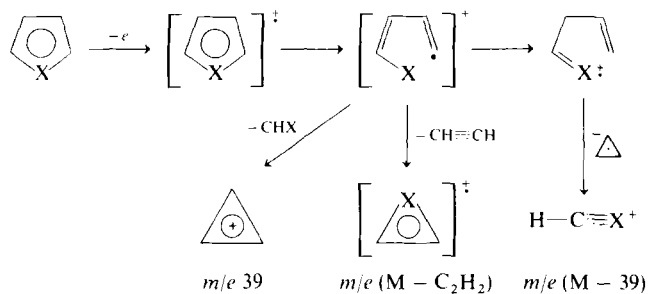
²³ M. Bavia, C. Zauli, and J. Fusina, *Mol. Phys.* **30**, 1289 (1975).

²⁴ S. L. N. G. Krishnamachari and T. V. Venkitachalam, *Chem. Phys. Lett.* **67**, 69 (1979).

²⁵ F. Fringuelli, G. Marino, A. Taticchi, G. Distefano, F. P. Colonna, and S. Pignataro, *J. C. S. Perkin II*, 276 (1976).

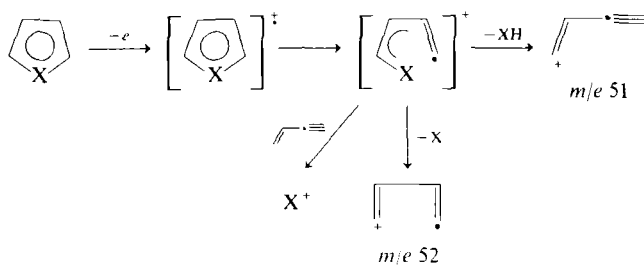
²⁶ L. N. Gunderova, L. S. Kostyuchenko, R. G. Latypova, N. M. Pozdeev, and L. M. Sverdlov, *Zh. Strukt. Khim.* **17**, 726 (1976).

²⁷ F. Fringuelli and A. Taticchi, *J. Heterocycl. Chem.* **15**, 137 (1978).



X = O, S, Se, Te

SCHEME 1



SCHEME 2

C. NMR SPECTROSCOPIC STUDIES

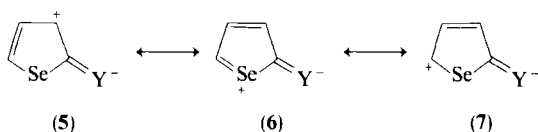
There are several systematic nuclear magnetic resonance studies of the interaction between the substituents and the protons and ring atoms of five-membered heterocycles. In some 2-substituted furans, thiophenes, selenophenes, and tellurophenes there is a linear correlation between the electronegativity of the chalcogen and several of the NMR parameters.²⁸ As there also is a good correlation between the shifts of the corresponding protons and carbons in the four heterocycles, the shifts of unknown selenophene and tellurophene derivatives can be predicted when those of thiophene are known. This is of special interest for the tellurophene derivatives, since they are difficult to synthesize. In the selenophene series, where a representative set of substituents can be introduced in the 2- as well as in the 3-position, the correlation between the ^1H and ^{13}C shifts and the reactivity parameters according to Swain and Lupton's two-parameter equation

²⁸ F. Fringuelli, S. Gronowitz, A.-B. Hörnfeldt, I. Johnson, and A. Taticchi, *Acta Chem. Scand., Ser. B* **B28**, 175 (1974).

could be studied.²⁹ Derivatives containing strongly electron-attracting or strongly electron-donating, as well as substituents of intermediate character such as methyl or the halogens, were chosen. Unequivocal shift assignments were in some cases obtained from deuterated derivatives. Both the direct and long-range couplings fall in well-defined intervals. The shifts caused by the substituents were compared with those of the corresponding thiophenes. Strong similarities between the two heterocycles were observed.

As one of the selenium isotopes, ⁷⁷Se, is NMR active, it has been possible to study the substituent-caused shifts of the heteroatom and selenium–proton couplings.³⁰ The assignments of the coupling constants are in most cases based on the proton spectra of the compounds, in which each band can normally be identified. The three coupling constants of 2-substituted selenophenes fall in well-defined intervals: $|J_{\text{Se-H}_5}| \gg |J_{\text{Se-H}_4}| > |J_{\text{Se-H}_3}|$. The signs of the spin–spin coupling constants $J(\text{H-H})$ and $J(\text{Se-H})$ have been obtained by double resonance experiments.³¹ The relative inductive and mesomeric contributions to the coupling constants are discussed. Substituent effects on these couplings are additive. The 2-halosubstituted selenophenes show ⁷⁷Se–proton couplings, which can be linearly correlated with the electronegativity of the haloatom. $J_{\text{Se-H}_5}$ increases with electronegativity, whereas $J_{\text{Se-H}_3}$ and $J_{\text{Se-H}_4}$ decrease. The carbonyl- and nitro-containing substituents show anomalously small downfield shifts and in some cases even upfield shifts compared with the parent compound. This observation was explained by a through-space binding interaction between Se *d*-orbitals and the carbonyl oxygen lone-pair in the *cis* conformation of the 2-carbonyl derivatives.³² Evidence from long-range coupling constant data shows that 2-formylselenophene exists almost exclusively in the Se–O *cis* conformation and 3-formyl-selenophene in the Se–O *trans* conformation (cf. Section IX,B).

Simple resonance theory suggests that for 2-substituted selenophenes the selenium atom can be considered to be situated in an ortho position and the influence of mesomeric and inductive effects or chemical shifts should be parallel for the 3-carbon (cf. resonance formula; **5–7** for *a*-I-M substituted derivative).



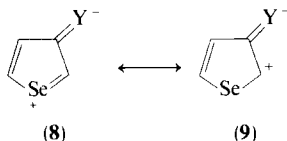
²⁹ S. Gronowitz, I. Johnson, and A.-B. Hörnfeldt, *Chem. Scr.* **7**, 111 (1975).

³⁰ S. Gronowitz, I. Johnson, and A.-B. Hörnfeldt, *Chem. Scr.* **3**, 94 (1973).

³¹ M. P. Simonnin, M. J. Pouet, J. M. Cense, and C. Paulmier, *Org. Magn. Reson.* **8**, 508 (1976).

³² S. Gronowitz, I. Johnson, and A.-B. Hörnfeldt, *Chem. Scr.* **8**, 8 (1975).

On the other hand, the situation is more complex for the 3-substituted derivatives. In such compounds the substituent can be considered electronically to be located either "meta" or "para" to the selenium ring atom (cf. resonance formulas **8** and **9** for a -I-M substituted derivative). However, the substituent-caused shifts in the 3-substituted derivatives indicate that the heteroatom and the substituents are para and not meta related. ^{77}Se chemical shifts are more sensitive than the ^{13}C shifts to changes in electron



density. For ^{13}C and ^{77}Se shifts, which are ortho related, $\Delta\text{C}/\Delta\text{Se}$ varies between 0.16–0.19, whereas for para-related shifts the ratio is 0.16. Based on the estimation that a unit charge causes about a 10-ppm shift for ^1H and 160-ppm for ^{13}C resonances, and that to a first approximation the electron density of similarly situated atoms is influenced in the same way by the substituents, this ratio would indicate a shift of 940 ppm unit charge for the ^{77}Se resonance.

Only in the 3-substituted series could the ^{77}Se shifts be correlated with the reactivity parameters of Swain and Lupton.³³

^{77}Se magnetic resonance has become a useful tool in the structure determination of selenium-containing compounds. The first chart of ^{77}Se chemical shifts in organic selenium compounds is given in Ref. 34. Selenophene has become more common as a reference substance³⁵ but a couple of other scales and standards are also currently in use.³⁶ However, these can easily be related to selenophene.

French workers have studied the ^1H - and ^{13}C -NMR parameters of disubstituted selenophenes.^{37,38} The proton chemical shifts are discussed in terms of magnetic anisotropy and electric field effects of the substituents in order to study the conformational equilibrium of the carbonyl group. The relationship between the ^1H - and ^{13}C -chemical shifts and π -electron distribution calculated by the PPP method are examined. Shifts and coupling constants are discussed in additivity terms.

³³ C. G. Swain and E. C. Lupton, Jr., *J. Am. Chem. Soc.* **90**, 4328 (1968).

³⁴ A. Fredga, S. Gronowitz, and A.-B. Hörnfeldt, *Chem. Scr.* **8**, 15 (1975).

³⁵ M. Baiwir, G. Llabrès, J.-L. Piette, and L. Christiaens, *Org. Magn. Reson.* **14**, 293 (1980).

³⁶ A. Fredga, S. Gronowitz, and A.-B. Hörnfeldt, *Chem. Scr.* **11**, 37 (1977).

³⁷ J. Morel, C. Paulmier, M. Garreau, and G. Martin, *Bull. Soc. Chim. Fr.*, 4497 (1971).

³⁸ M. Garreau, G. J. Martin, M. L. Martin, J. Morel, and C. Paulmier, *Org. Magn. Reson.* **6**, 648 (1974).

These authors have also reported an NMR study of various Grignard reagents, derived from bromopyridine, furan, thiophene, and selenophene.³⁹ The NMR parameters relate to electronic structure. The exchange reactions between heterocyclic bromides and isopropylmagnesium chloride were followed by NMR, and the activation parameters were determined for the rate-determining step of the formation of the Grignard reagent of the heterocycles. A number of monosubstituted selenophenes have been the subject of a theoretical study concerning the nuclear spin coupling constants and hyperfine coupling constants.⁴⁰ The calculated nuclear spin coupling constants are in good agreement with the experimental values with regard to signs, magnitudes, internal orders, and some trends.

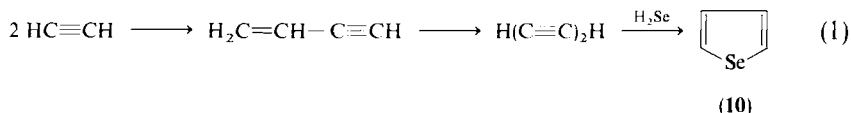
D. ELECTRON SPECTROSCOPY FOR CHEMICAL ANALYSIS

During the last decade one paper concerning the use of ESCA on heterocyclic compounds has appeared. The observed effects are interpreted in terms of intramolecular charge-transfer transitions between a donor and an acceptor group of the molecule.⁴¹

VI. Preparation of Selenophenes

A. FROM ACYCLIC COMPOUNDS

One of the reasons for the slow development of selenophene chemistry was the lack of convenient procedures for obtaining selenophene, its homologs, and derivatives. However, Gronowitz *et al.*⁴² have reported a semilarge-scale synthesis of selenophene (10), which gives about 150–200 g (~58% yield) of selenophene per day. The procedure is a pyrolytic reaction



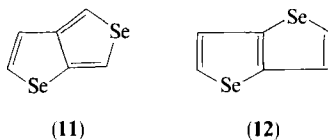
³⁹ G. J. Martin, B. Mechin, Y. Leroux, C. Paulmier, and J. C. Meunier, *J. Organomet. Chem.* **67**, 327 (1974).

⁴⁰ V. Galasso and A. Bigotto, *Org. Magn. Reson.* **6**, 475 (1974).

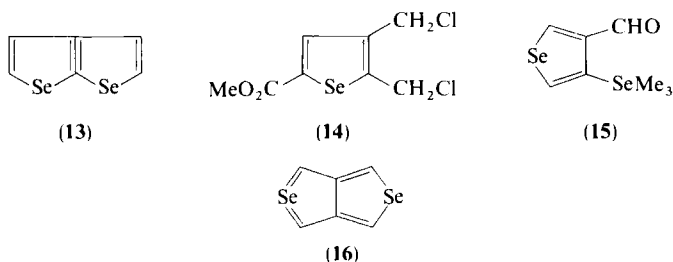
⁴¹ S. Pignataro and G. Destefano, *Z. Naturforsch., A* **30A**, 815 (1975).

⁴² S. Gronowitz, T. Frejd, A. Moberg-Ogard, and L. Tregge, *J. Heterocycl. Chem.* **13**, 1319 (1976).

between acetylene and selenium mixed with alumina. Selenophene is believed to originate from the addition of hydrogen selenide to diacetylene as shown in Eq. (1). Alumina seems mainly to have an area-increasing effect, since only when the alumina pellets become completely covered with tarry material are good yields obtained. In this reaction, about 30 other components were identified, including 2- and 3-alkylselenophene, 2- and 3-alkylselenoselenophene, biselenienyls, benzo[*b*]selenophene, and tricyclic-fused systems.⁴³ In other work on the reaction between acetylene and selenium Umezawa claimed that the major by-product (mp 123–124.5°C) was selenolo[3,4-*b*]selenophene (11).⁴⁴ The structure determination was mainly based on dipole moment measurements. However, by a combination of mass spectroscopy, ¹³C and ⁷⁷Se NMR, and dipole moment measurements it was later demonstrated that this substance is in fact selenolo[3,2-*b*]selenophene (12).⁴⁵



Selenolo[3,2-*b*]selenophene (12) and selenolo[2,3-*b*]selenophene (13) have been synthesized from lithium derivatives of 2-(3-bromo-2-selenienyl) 1,3-dioxane and 2-(3-selenienyl) 1,3-dioxane, respectively, by reaction with selenium and methyl chloroacetate followed by Dieckmann cyclization.⁴⁶ Even the third "classical" selenophthene (11) has been synthesized by two different routes, using 2,3-bischloromethyl-5-carbomethoxyselenophene (14) or preferably 4-methylseleno-3-selenophene aldehyde (15).⁴⁶ The fourth selenophthene isomer (16), which has a nonclassical structure, has not yet been obtained in spite of great efforts.⁴⁷



⁴³ S. Gronowitz, A. Konar, and A.-B. Hörnfeldt, *Chem. Scr.* **10**, 159 (1976).

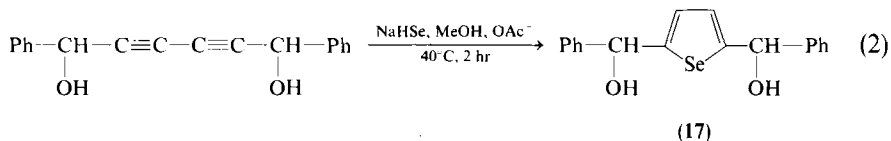
⁴⁴ S. Umezawa, *Bull. Chem. Soc. Jpn.* **14**, 363 (1939).

⁴⁵ S. Gronowitz, T. Frejd, and A.-B. Hörnfeldt, *Chem. Scr.* **5**, 236 (1974).

⁴⁶ A. Konar and S. Gronowitz, *Tetrahedron* **36**, 3317 (1980).

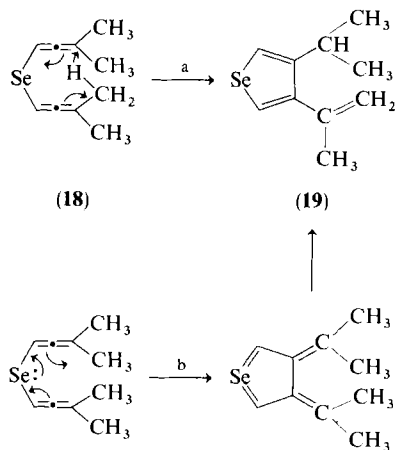
⁴⁷ S. Gronowitz and A. Konar, *J. C. S. Chem. Commun.*, 163 (1977).

A more general synthesis of selenophene derivatives, starting from diacetylenes and sodium hydrogen selenide, was investigated by Curtis.⁴⁸ In the synthesis of new tetraphenylporphyrin molecules containing heteroatoms other than nitrogen, Ulman *et al.*⁴⁹ used in principle the method of Curtis for the synthesis of the starting material (17).



Selenophene was also obtained as the main component in the reaction between vinylacetylene and the selenium dianion, generated from elemental selenium (Se_8), in dimethyl sulfoxide-potassium-water at $100\text{--}120^\circ\text{C}$.⁵⁰

Bis- γ,γ -dimethylallenyl selenide (18) is converted by spontaneous cycloaromatization to 3-isopropenyl-4-isopropylselenophene (19).⁵¹ Two mechanisms are shown in Scheme 3.



SCHEME 3

In a semimicro synthesis selenophene is prepared from bis(trimethylsilyl)-1,3-butadiyn and NaHSe generated *in situ* from Se and NaBH_4 in aqueous dimethylformamide.⁵² Other ring cyclization reactions have been performed

⁴⁸ R. F. Curtis, S. N. Hasnain, and J. A. Taylor, *J. C. S. Chem. Commun.*, 365 (1968).

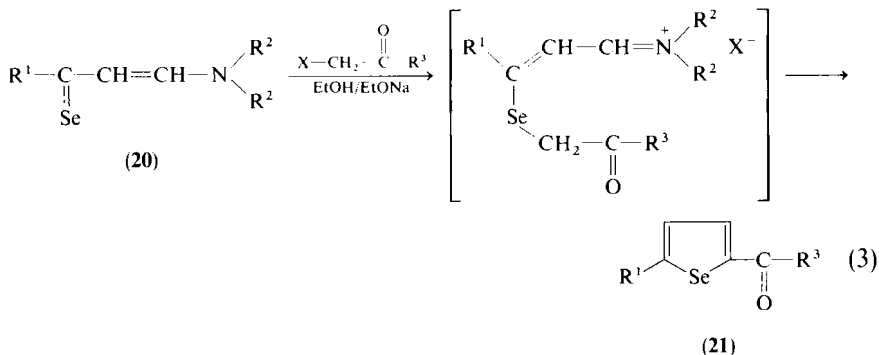
⁴⁹ A. Ulman, J. Manassen, F. Frolow, and D. Rabinovich, *Tetrahedron Lett.*, 167 (1978).

⁵⁰ B. A. Trofimov, G. K. Musorin, G. A. Kalabin, and S. V. Amosova, *Zh. Org. Khim.* **16**, 518 (1980).

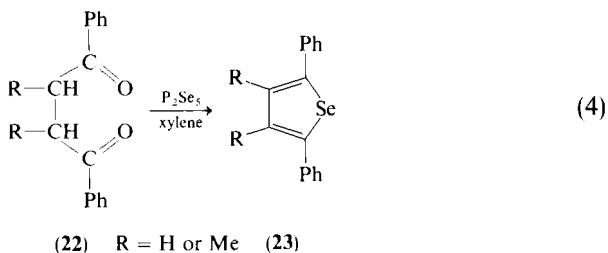
⁵¹ S. Braverman and Y. Duar, *Tetrahedron Lett.*, 1493 (1978).

⁵² P. M. Jacobs, M. A. Davis, and H. Norton, *J. Heterocycl. Chem.* **14**, 1115 (1977).

by Mamedov *et al.*⁵³⁻⁵⁵ Thus, selenophene was prepared in 45% yield by cyclizing butadiene with selenium dioxide at 500°C in the presence of zeolite-rare earth catalysts. Liebscher and Hartman^{56,57} have developed a procedure, shown in Eq. (3), for the preparation of 2,5-disubstituted selenophenes (**21**) via 2-aminovinyl seleno ketones (**20**).



Phosphorus pentaselenide prepared from red, amorphous selenium effects cyclization of 1,4-diketones (**22**) to substituted selenophenes (**23**) in moderate



yields.⁵⁸ This reaction is a more general way to 2,5-disubstituted selenophenes than those previously mentioned. Another ring closure is the Fiesselmann reaction,^{59,60} involving aldehyde **24** in Eq. (5), sodium selenide,

⁵³ E. Sh. Mamedov, S. B. Kurbanov, R. D. Mishiev, and T. N. Shakhtakhtinskii, *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki* **55**, 74 (1978).

⁵⁴ E. Sh. Mamedov, S. B. Kurbanov, R. D. Mishiev, and T. N. Shakhtakhtinskii, *Dokl. Akad. Nauk Az. SSR* **34**, 41 (1978).

⁵⁵ E. Sh. Mamedov, S. B. Kurbanov, R. D. Mishiev, and T. N. Shakhtakhtinskii, *Zh. Org. Khim.* **15**, 1554 (1979).

⁵⁶ J. Liebscher and H. Hartmann, *Synthesis*, 521 (1976).

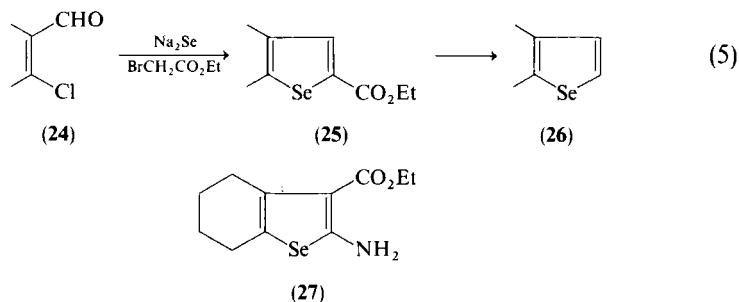
⁵⁷ J. Liebscher and H. Hartmann, East German Patent 123,665 (1975).

⁵⁸ S. Gronowitz and A. Konar, *Chem. Scr.* **12**, 11 (1977).

⁵⁹ P. Cagniant, P. Périn, G. Kirsch, and D. Cagniant, *C. R. Acad. Sci. Ser. C* **277**, 37 (1973).

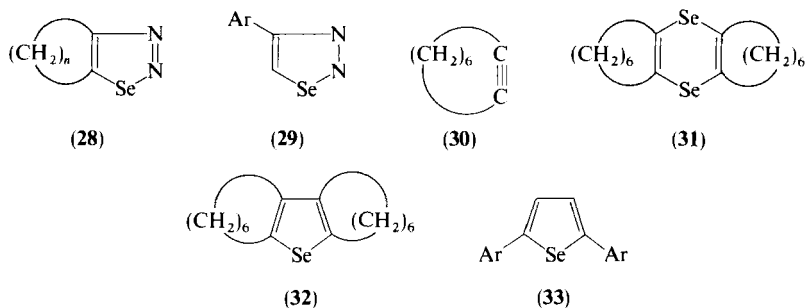
⁶⁰ P. Cagniant, P. Périn, and G. Kirsch, *C. R. Acad. Sci., Ser. C* **278**, 1201 (1974).

and ethyl bromoacetate to give 2,3-disubstituted selenophenes (**26**). In the Gewald reaction cyclohexanone, ethyl cyanoacetate, and selenium in the presence of base give compound **27**.⁶¹



B. FROM OTHER RING SYSTEMS

Lalezari and co-workers prepared selenophene derivatives from cycloalka-1,2,3-selenadiazoles (**28**) and 4-phenyl-1,2,3-selenadiazoles (**29**) by pyrolysis. When **28** ($n = 6$) was pyrolyzed in boiling toluene or carbon tetrachloride, compounds **30** and **31** were obtained.⁶² When **31** was heated to 250°C, dicyclooctaselenophene (**32**) was smoothly formed. For the preparation of 2,5-diarylselenophenes (**33**), derivatives **29** were used.⁶³ 4-Phenyl-1,2,3-selenadiazole, gave only 2,5-diphenylselenophene at 140°C, whereas at higher temperatures (240–250°C) 2,5-diphenylselenophene was the major product, along with small quantities of 2,4-diphenylselenophene. Perhaps 1,2,3-selenadiazole first decomposes to the monoaryl-substituted acetylene and selenium. In the second step, monoaryl-substituted acetylenes and

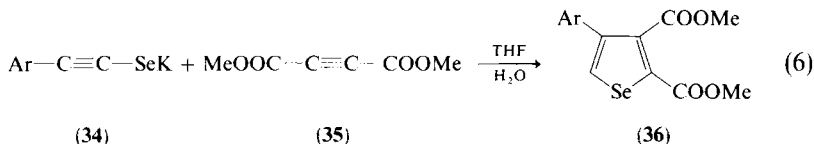


⁶¹ S. M. Karipak, A. A. Dobosh, I. V. Smolanka, and A. S. Mikitchin, *Khim. Geterotsikl. Soedin.*, **Sb. 9**, 326 (1973).

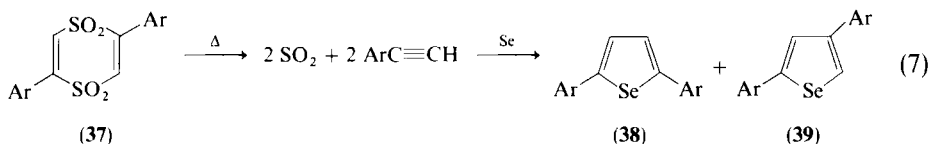
⁶² I. Lalezari, A. Shafiee, and M. Yalpani, *J. Heterocycl. Chem.* **9**, 1411 (1972).

⁶³ I. Lalezari, A. Shafiee, F. Rabet, and M. Yalpani, *J. Heterocycl. Chem.* **10**, 953 (1973).

selenium interact and afford the corresponding selenophenes. Similarly, potassium 2-arylethylene selenolate (**34**), prepared from 4-aryl-1,2,3-selenadiazoles (**29**), undergoes 1,3-polar cycloaddition with dimethyl acetylenedicarboxylate (**35**) to give dimethyl 4-arylselenophene-2,3-dicarboxylate (**36**) in 30–50% yield (Eq. 6).⁶⁴ Considering these results and the fact that



displacement of sulfone groups by selenium is a well-known reaction in dibenzo-1,4-dithiin 1,1,4,4-tetroxide, giving high yields of dibenzo-1,4-diselenine, the thermal reaction of selenium and 2,5-diaryl-1,4-dithiin 1,1,4,4-tetroxide (**37**) was studied.⁶⁵ However, 2,5-diaryl-1,4-diselenine was not formed, but mainly 2,5-diarylselenophene (**38**) and a small quantity of 2,4-diarylselenophene (**39**). The reaction sequence shown in Eq. (7) was suggested to account for their formation.



VII. Electrophilic and Nucleophilic Substitution Reactions

A. COMPARATIVE STUDIES

Electrophilic substitution in furan, thiophene, selenophene and pyrrole has, up to 1970, been comprehensively reviewed by Marino.⁶⁶ Italian workers have determined the relative reactivities of selenophene and thiophene as well⁶⁷; relative rates are given in Table I. Including furan, the order of reactivity is furan > selenophene > thiophene.

Formylation of aromatic substrates with the dimethylformamide-carbonyl chloride complex in chloroform⁶⁸ demonstrates simple kinetics.⁶⁹

⁶⁴ A. Shafiee, I. Lalezari, and F. Savabi, *Synthesis*, 765 (1977).

⁶⁵ I. Lalezari, A. Shafiee, and A. Rashidbaigi, *J. Heterocycl. Chem.* **13**, 57 (1976).

⁶⁶ G. Marino, *Adv. Heterocycl. Chem.* **13**, 235 (1971).

⁶⁷ P. Linda and G. Marino, *J. Chem. Soc. B*, 43 (1970).

⁶⁸ S. Clementi, F. Fringuelli, P. Linda, G. Marino, G. Savelli, and A. Taticchi, *J. C. S. Perkin II*, 2097 (1973).

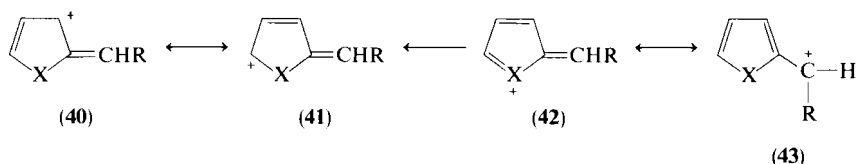
⁶⁹ S. Alunni, P. Linda, G. Marino, S. Santini, and G. Savelli, *J. C. S. Perkin II*, 2070 (1972).

TABLE I⁶⁷
RELATIVE RATES OF ELECTROPHILIC SUBSTITUTION FOR
SELENOPHENE AND THIOPHENE

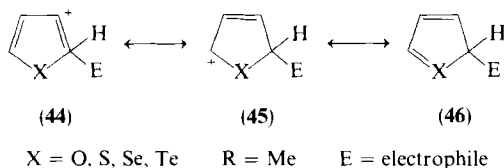
| Reaction conditions | k_s/k_t |
|---|-----------|
| Bromination, Br ₂ , AcOH, 25°C | 47.5 |
| Chlorination, Cl ₂ , AcOH, 25°C | 6.5 |
| Bromination, HOBr, HClO ₄ , 50% dioxane, 25°C | 4.5 |
| Trifluoroacetylation, (CF ₃ CO) ₂ O, dichloroethane, 75°C | 6.6 |
| Acetylation, Ac ₂ O + SnCl ₄ , dichloroethane, 25°C | 1.9 |

However, the rate of substitution of pyrrole is too high and that of benzene too low to be followed by standard techniques, and consequently a kinetic study was limited to furan, thiophene, selenophene, and tellurophene. Activation entropies are constant for all four members of the series, indicating that the arrangement of the atoms around the reaction center is similar, i.e., the transition states of all four rings occur at similar positions along the reaction coordinate. The relative rates for the formylation are thus controlled by the activation enthalpies. At 30°C relative rates are furan (107), thiophene (1), selenophene (3.64), and tellurophene (36.8).⁶⁸

Electrophilic aromatic substitution has been compared with side-chain solvolysis of 1-arylethyl esters, and it has been stated that there is complete parallelism between these two types of reaction.⁷⁰ A comparison of the rate constants for the solvolysis of 1-arylethyl acetates, where the aryl groups are the four heterocyclic rings containing the group VI elements and the relative rates for the acetylation reaction of the unsubstituted rings has been made. However, reactivity in solvolysis and acetylation is not the same. An inversion between furan and tellurophene is observed. The main difference between the two reactions lies in the presence of an extra mesomeric structure (43) in describing the resonance hybrid of the intermediate formed by solvolysis. Moreover, electronegativity or polarizability may play a fundamental role in stabilizing the intermediate carbonium ions and, consequently, in determining the relative rates in different ways in the two types of reaction. Whereas electrophilic substitution rates are linearly correlated with the

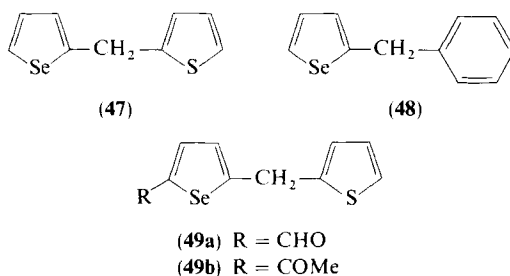


⁷⁰ S. Clementi, F. Fringuelli, P. Linda, G. Marino, G. Savelli, and A. Taticchi, *Gazz. Chim. Ital.* **107**, 339 (1977).

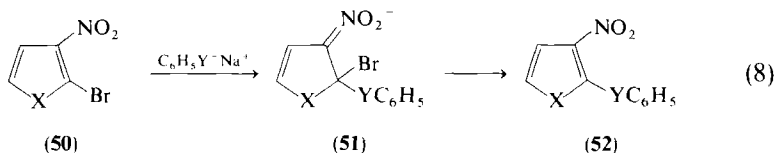


resonance energies of the four rings, the rates of the side-chain reactions follow the electronegativity of the heteroatom.

Substrates **47** and **48** have also been used to study the relative reactivities of selenophene and thiophene and of selenophene and benzene.⁷¹ The higher reactivity of the selenophene ring was demonstrated by the fact that upon formylation 59% of compound **49a** was formed and upon acylation 63% of derivative **49b**. Acylation of **48** gave exclusively 2-acetyl-5-benzylselenophene. Structures of the products were determined by ¹H NMR.



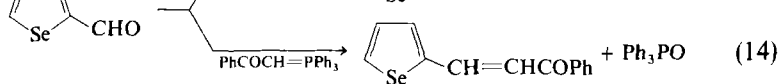
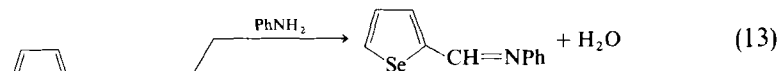
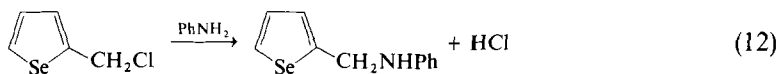
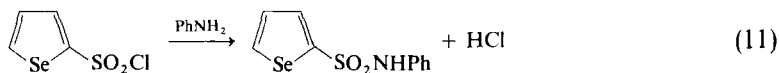
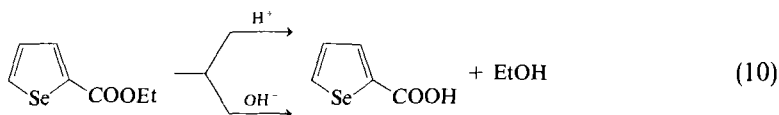
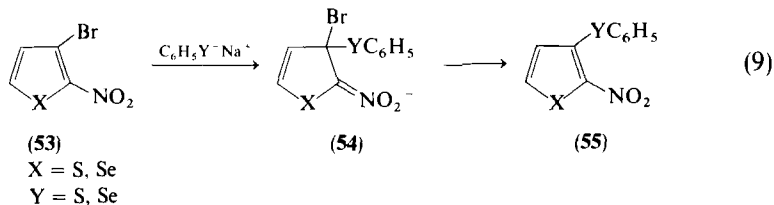
Nucleophilic substitution reactions in the selenophene series have attracted some interest. Debromination of bromonitro compounds [(**50**, X = S, Se) and (**53**, X = S, Se)] with sodium thiophenoxide and sodium selenophenoxide⁷² was studied. Selenophene compounds were four times more reactive than the thiophene derivatives. The position of attack, α or β , had very little influence on the rate ratio. The kinetics of the side-chain nucleophilic reactions of selenophene derivatives, shown in Scheme 4, has been reported.⁷³



⁷¹ P. A. Konstantinov, N. M. Koloskova, R. I. Shupik, and M. N. Volkov, *Zh. Obshch. Khim.* **43**, 872 (1973).

⁷² G. Guanti, C. Dell'Erba, and G. Garbarino, *J. Heterocycl. Chem.* **7**, 1425 (1970).

⁷³ A. Arcoria, E. Maccarone, and A. Mamo, *J. C. S. Perkin II*, 1347 (1979).



SCHEME 4

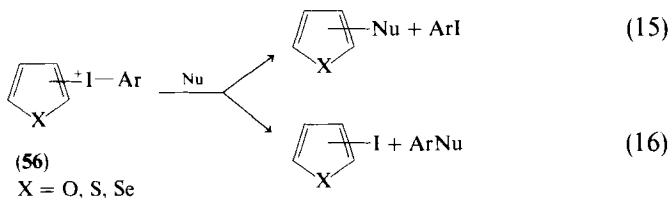
The greatest difference observed between the side-chain reactivities of selenophene and thiophene derivatives was in the reaction of aldehydes with aniline (cf. Eq. 13), a ratio of ~ 4.2 .

Selenophene compounds react faster than the corresponding thiophene derivatives in both electrophilic and nucleophilic substitutions. This may be due to the capacity of selenophene to delocalize both positive and negative charges, since the selenium atom is larger and more polarizable than the sulfur atom and consequently selenophene can release its *p*-electrons and accept electrons into its free *d*-orbitals more readily than thiophene.

B. INVERTED REACTIVITY OF ARYLLITHIUM DERIVATIVES

Organolithium derivatives are strongly nucleophilic reagents, and their use in synthesis would be greatly increased if they could easily be converted to electrophilic reagents. Reversed reactivity of lithium derivatives would be

of great value for the synthesis of nitro, amino, and alkoxy derivatives, which are not conveniently available by direct reaction of organolithium compounds with suitable reagents, and also for the arylation of active methylene derivatives. Gronowitz and Holm have used diaryliodonium salts (56) as



reagents with such reversed reactivity. Metalation of selenophene with butyllithium followed by reaction with *trans*-iodosovinyl dichloride gave di-(2-selenienyl)iodonium chloride, which upon reaction with sodium nitrite in *N,N*-dimethylformamide gave pure 2-nitroselenophene.⁷⁴ 3-Bromoselenophene gave both the iodonium salt and 3-nitroselenophene in lower yields than the 2-isomer, which could in part be due to ring-opening reactions (cf. Section VII,B). By changing the nucleophile to sodium thiocyanate 3-thiocyanoselenophene was also obtained.⁷⁵

VIII. Reactions via Organometallic Intermediates

A. METALATION AND HALOGEN-METAL EXCHANGE

It is well-known that 2- and 3-selenienyllithium derivatives are valuable synthetic intermediates for the preparation of various 2- and 3-substituted selenophenes. In this way, 2- and 3-chloroselenophenes have been obtained by reaction with hexachloroethane at -70°C .⁷⁶ Another example has already been shown in connection with inverted reactivity (Section VI,B), and many applications will be demonstrated in subsequent sections.

B. RING-OPENING REACTIONS

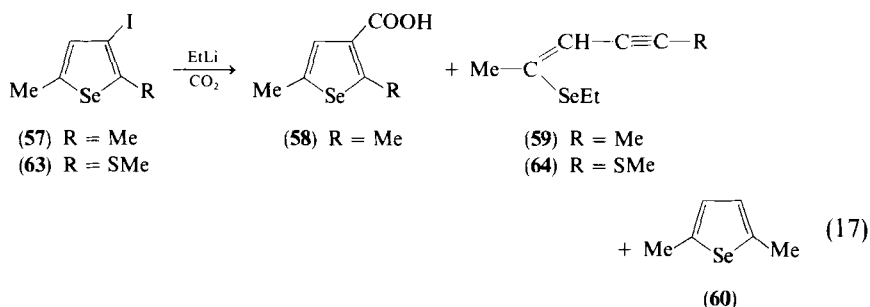
By comparison with the corresponding thiophenes, the tendency to ring opening is greater in the selenophene series. One of the first examples was the unexpected observation that 2,2',5,5'-tetramethyl-3,3'-biselenienyl was

⁷⁴ S. Gronowitz and B. Holm, *Synth. Commun.* **4**, 63 (1974).

⁷⁵ S. Gronowitz and B. Holm, *J. Heterocycl. Chem.* **14**, 281 (1977).

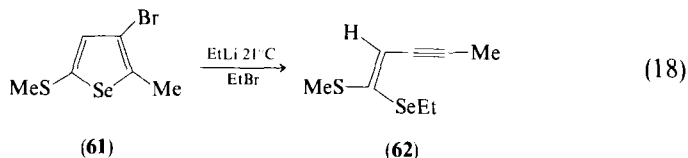
⁷⁶ S. Gronowitz, A.-B. Hörnfeldt and K. Pettersson, *Synth. Commun.* **3**, 213 (1973).

not formed in the reaction of ethyllithium with 2,5-dimethyl-3-iodoselenophene (**57**) and subsequent treatment with copper chloride at -70°C .⁷⁷ This coupling reaction works extremely well in the thiophene series and has been used in a number of cases for the preparation of bithienyls. 2,5-Dimethyl-3-selenienyllithium with carbon dioxide at -70°C , gave carboxylic acid (**58**); and an alicyclic vinylacetylene (**59**) (49%) is formed in addition to dimethylselenophene (**60**) (Eq. 17). It was possible to trap the 3-selenienyllithium derivative as the carboxylic acid (**58**) (51%) at -100°C .



This lithiated species is thus, in all likelihood, an intermediate in the ring-opening reaction.⁷⁸ The thermal ring opening of 3-selenienyl-, 3-thienyl-, and 2,5-dimethyl-3-furyllithium has also been examined.⁷⁹ Several factors influence the halogen-metal exchange, the metalation, and the ring-opening reaction (e.g., the nature of the heteroatom, the ring substituents, the lithium reagent, and to some extent also the mode of addition of the lithium reagent). The solvents might also be of some importance.

The reaction of 3-bromo-5-(methylthio)-2-methylselenophene (**61**) with ethyllithium and ethyl bromide (Eq. 18) gives mixed thioselenoacetals of an acetylenic ketene (**62**) in high yield.⁸⁰ Similarly, isomeric 3-bromo-5-methyl-2-(methylthio)selenophene (**63**) is also easily cleaved to give 2-ethylseleno-5-methylthio-2-hepten-4-yne (**64**) (Eq. 17). Such compounds are difficult to obtain by other methods.



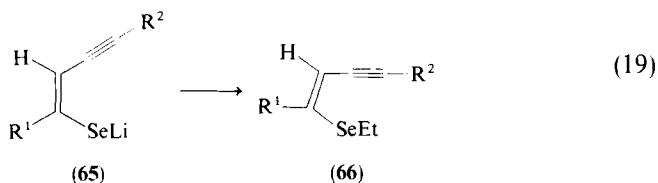
⁷⁷ S. Gronowitz and T. Frejd, *Acta Chem. Scand.* **23**, 2540 (1969).

⁷⁸ S. Gronowitz and T. Frejd, *Acta Chem. Scand.* **24**, 2656 (1970).

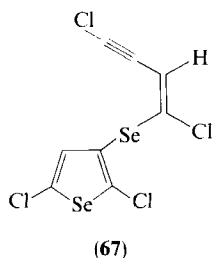
⁷⁹ S. Gronowitz and T. Frejd, *Int. J. Sulfur Chem., Part A* **2**, 165 (1972).

⁸⁰ S. Gronowitz and T. Frejd, *Acta Chem. Scand.* **27**, 2242 (1973).

Ring opening of 3-selenienyllithium derivatives with nonidentical alkyl groups in the α - and α' -positions led to **65** which can be alkylated by ethyl bromide to give ethylselenovinylacetylenes (**66**) (Eq. 19) with the (*Z*)-configuration.⁸¹ Ring opening takes place in a trans manner leading to selenoenynes with the heteroatom and the triple bond in a cis arrangement.



The reaction of 2,5-dichloro-3-iodoselenophene with ethyllithium gave **67**.⁸² Attack of the initially formed 2,5-di-chloroselenienyllithium on the



selenium atom of another molecule resulted in ring opening and elimination of iodide ion. A similar reaction involving a 2-selenienyllithium intermediate was observed with 2,3,5-tribromoselenophene and butyllithium in THF at -110°C . The formation of diphenylselenide upon treatment of tetrachloroselenophene with excess phenyllithium was also attributed to such a reaction.⁸³ 2,5-Dichloroselenophene with diisopropylaminolithium, however, gave the stable compound 2,5-dichloro-3-selenienyllithium.⁸²

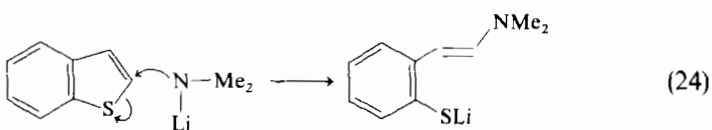
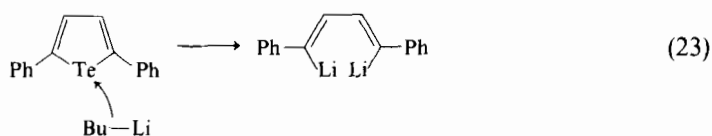
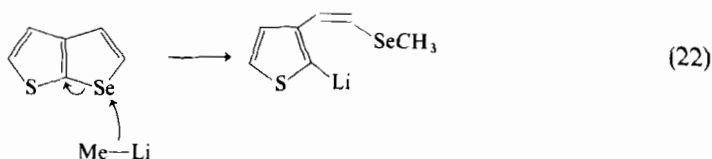
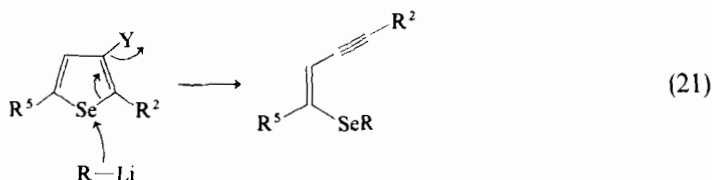
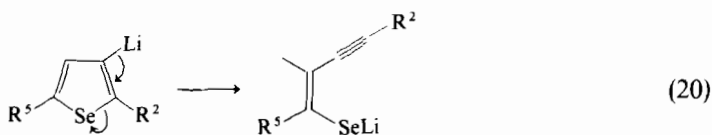
The above-mentioned and other base-promoted ring-opening reactions can be divided into some characteristic types (Scheme 5). These and other base-induced, ring-opening reactions have been systematized and reviewed recently.⁸⁴ Such ring-opening reactions are very common. However, applications to the thiophene and selenophene series have not been extensive. Most ring-opening reactions are of the eliminative ring fission type (Eqs. 20 and 21, Scheme 5) and are of synthetic interest. Using heterocycles as matrices

⁸¹ S. Gronowitz and T. Frejd, *Acta Chem. Scand., Ser. B* **B30**, 313 (1976).

⁸² S. Gronowitz and T. Frejd, *Acta Chem. Scand., Ser. B* **B30**, 439 (1976).

⁸³ T. Frejd, *Chem. Scr.* **10**, 133 (1976).

⁸⁴ S. Gronowitz and T. Frejd, *Chem. Heterocycl. Comp. (Engl. Transl.)* **14**, 353 (1978).



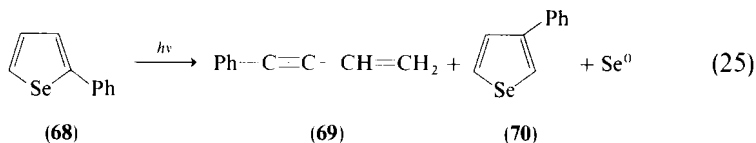
SCHEME 5

for various substituents to be introduced at certain positions, one can employ ring opening to obtain compounds that are often difficult to synthesize by other methods. This is particularly true considering the high regio- and stereospecificity of these reactions.

Substitutional ring openings seem to be more unusual (Eqs. 22–24, Scheme 5). The reactions of 2,5-dimethoxyselenophene with butyl- and phenyllithium have been examined.⁸⁵ In view of the formation of dibutyl- and diphenylselenide, respectively, together with some dienes, a logical reaction sequence could be formulated in which the first step is an attack on the selenium atom by the lithium reagent. Nonfused selenophenes are also cleaved in a substitution-type reaction.

⁸⁵ S. Gronowitz, A. Hallberg, and T. Frejd, *Tetrahedron* **35**, 2607 (1979).

Another type of ring opening has been demonstrated by Barton *et al.*⁸⁶ in their study of the photochemistry of 2-phenylselenophene. Upon irradiation, 2-phenylselenophene (**68**) gives a mixture of 3-phenylselenophene (**70**), phenylvinylacetylene (**69**), and selenium (Eq. 25).

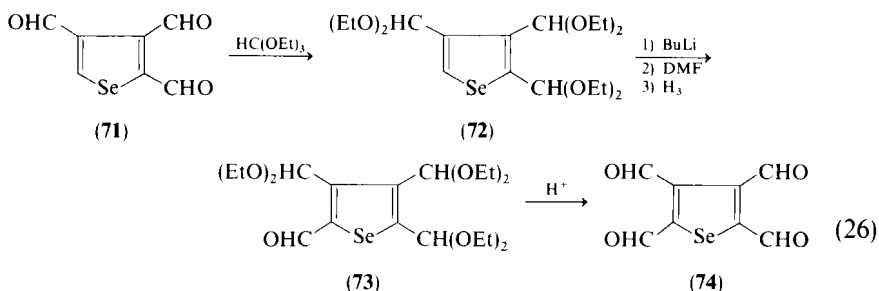


IX. Carbonyl-Substituted Derivatives of Selenophene

A. PREPARATION AND REACTIONS OF FORMYLSELENOPHENES

The formyl group is generally introduced via the Vilsmeier reaction by dimethylformamide in the presence of phosphorus oxychloride, by the Sommelet reaction via the corresponding chloromethyl derivative, or by treating the lithio compound with dimethylformamide.⁸⁷

The latter is illustrated by the preparation of the previously unknown tetraformylselenophene by Morel (Eq. 26).⁸⁸ The formyl group has also been introduced by treating dibromoselenophenes with copper cyanide in quinoline and reduction of the dicyano derivative obtained.⁸⁹



By a combination of direct metalation and halogen-metal exchange, and by protecting the initially introduced formyl groups, the isomeric triformyl derivatives were prepared.^{89,90} Oxidizing one of the formyl groups gives

⁸⁶ T. J. Barton, C. R. Tully and R. W. Roth, *J. Organomet. Chem.* **108**, 183 (1976).

⁸⁷ V. I. Dulencko and N. N. Alekseev, *Khim. Geterotsikl. Soedin.*, **9**, 918 (1973).

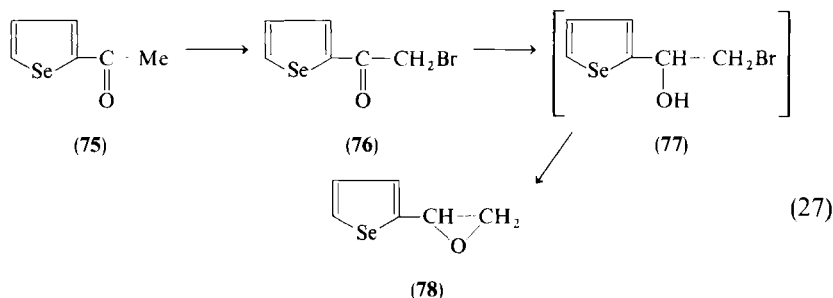
⁸⁸ J. Morel, C. Paulmier, and P. Pastour, *C. R. Acad. Sci., Ser. C* **269**, 37 (1969).

⁸⁹ C. Paulmier, J. Morel, and P. Pastour, *Bull. Soc. Chim. Fr.*, 2511 (1969).

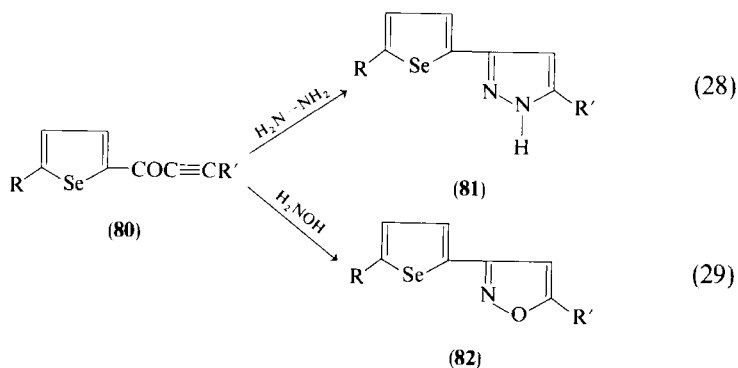
⁹⁰ B. Decroix, J. Morel, C. Paulmier, and P. Pastour, *Bull. Soc. Chim. Fr.*, 1848 (1972).

the diformyl-2-selenophenecarboxylic acids. Selenophene-2,5-dicarboxylic acid has been obtained by oxidation of 2,5-dimethylselenophene.⁹¹

Different 5-alkyl-2-formyl- and 5-alkyl-2-acetylselenophenes have been synthesized as well as semicarbazones derived from them.⁹² The acetyl derivatives have in the following reaction sequence (Eq. 27) been used for preparation of epoxyselenophenes.⁹³



Selenienylalkynylcarbinols were prepared by the addition of Grignard reagents or the sodium salts of acetylenes to 2-formylselenophene and its derivatives. The alcohols were oxidized and the resulting ketones treated with hydrazine and hydroxylamine to give the diheteroaryls **81** and **82**.⁹⁴



Triheteroaryls are obtained from β -diketones (such as **83**) from 3-acetylselenophene condensed with suitable methyl esters.⁹⁴ However, it was

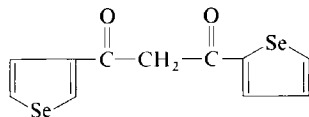
⁹¹ P. A. Konstantinov, T. V. Shchedrinskaya, and I. V. Zakharov, *Khim. Geterotsikl. Soedin.*, **Sb. 8**, 1605 (1972).

⁹² N. N. Alekseeva, S. N. Baranov, and V. I. Dulenko, *Khim. Geterotsikl. Soedin.*, **Sb. 7**, 31 (1971).

⁹³ N. N. Magdesieva and T. A. Balashova, *Khim. Geterotsikl. Soedin.*, **Sb. 6**, 716 (1970).

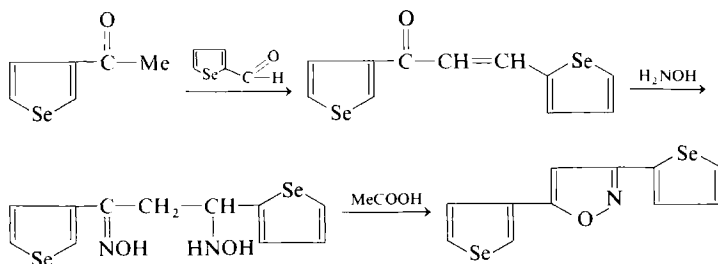
⁹⁴ A. S. Nakhmanovich, V. N. Elokhina, and R. V. Karnaukhova, *Khim. Geterotsikl. Soedin.*, **Sb. 7**, 920 (1971).

impossible to obtain di(3-selenenoyl)methane by condensing 3-acetylsephenophene with methyl 3-selenophenecarboxylate. The β -diketones are then ring closed with hydrazine.⁹⁵ The direction of the enolization of these β -diketones is substituent dependent. Compound **83**, for example, enolizes at the carbonyl group adjacent to the 2-selenienyl moiety, whereas when this 2-selenienyl ring is replaced by phenyl, enolization is at the other carbonyl group.⁹⁶



(83)

Selenienyl-substituted isoxazoles are obtained by first condensing acetyl- and formylselenophenes to give α,β -unsaturated ketones which when treated with hydroxylamine give hydroxamino oximes. Ring closure follows in the presence of acetic acid⁹⁶ (Scheme 6).



SCHEME 6

The proton-acceptor capability of some 2-acetylselenophenes in dilute sulfuric acid has been determined by the ^1H NMR method.⁹⁷ With phenol as proton donor, hydrogen-bond formation can be studied using IR spectroscopy as the analytical method.⁹⁸ Intramolecular hydrogen-bond formation

⁹⁵ Yu. K. Yur'ev, N. N. Magdesieva, and A. T. Monakhova, *Khim. Geterotsikl. Soedin.*, **Sb. 4**, 650 (1968).

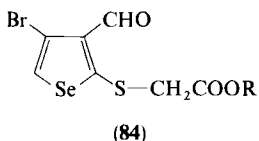
⁹⁶ Yu. K. Yur'ev, N. N. Magdesieva, and A. T. Monakhova, *Khim. Geterotsikl. Soedin.*, **Sb. 4**, 645 (1968).

⁹⁷ S. V. Tsukerman, L. P. Pivovarevich, L. A. Kutulya, V. G. Gordienko, N. N. Magdesieva, and V. F. Lavrushin, *Zh. Obshch. Khim.* **45**, 1070 (1975).

⁹⁸ Yu. N. Surov, L. P. Pivovarevich, L. A. Kutulya, Yu. A. Sukach, N. N. Magdesieva, and S. V. Tsukerman, *Zh. Obshch. Khim.* **46**, 2437 (1976).

has also been studied by ^1H NMR, selenophene derivatives being compared with other five-membered heterocycles.⁹⁹

The formyl group in orthoformylselenophenecarboxylic acids on reduction to an hydroxymethyl group undergoes ring closure to lactones.¹⁰⁰ To obtain 2,4-disubstituted selenophenes, 4-bromo-2-formylselenophene was prepared by the swamping catalyst method.¹⁰¹ Selenopheno[2,3-*b*]thiophene derivatives may be prepared from compound **84**.¹⁰² Another route to substituted



selenolothiophenes is via selenienylpropenoic acids obtained from Wittig reactions of the corresponding aldehyde.¹⁰³ A variety of selenienyl diketones has been prepared by addition of selenienyllithium compounds to formylselenophenes, followed by oxidation of the resulting alcohols.^{104,105} In an attempt to reduce 2-selenienyl 2-thienyl ketone by Wolff-Kishner reduction, both the methylene derivative and 2-(pentenyl)thiophene were obtained.¹⁰⁶

B. CONFORMATIONS OF 2-FORMYL- AND 2-ACETYLSELENOPHENES

Studies of the conformations of 2-formyl and 2-acetyl derivatives of the five-membered heterocycles have attracted great interest in recent years, but some of the results have been contradictory. At low temperatures the inter-conversion of the two conformers, *trans*-**85** and *cis*-**86**, is slow, and can be studied by NMR. Thus, the ^1H -NMR spectra of some selenophene deriva-

⁹⁹ L. N. Kurkovskaya, N. N. Shapet'ko, I. Ya. Kvitko and N. B. Sokolova, *V Sb., XI Medeleevsk. S'ezd po Obshch. i Prikl. Khim. Ref. Dokl. i Soobshch.*, 56 (1975).

¹⁰⁰ C. Paulmier, J. Bourguignon, J. Morel, and P. Pastour, *C. R. Acad. Sci. Ser. C* **270**, 494 (1970).

¹⁰¹ V. I. Dulenko and N. N. Alekseev, *Khim. Geterotsikl. Soedin.*, 918 (1973).

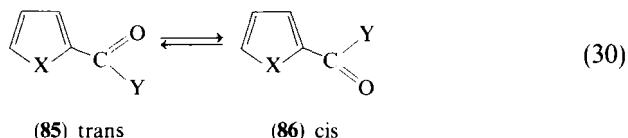
¹⁰² Ya. L. Gol'dfarb, I. P. Konyaeva, and V. P. Litvinov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1570 (1974).

¹⁰³ B. Capron, C. Paulmier, and P. Pastour, *Bull. Soc. Chim. Fr.*, 2575 (1975).

¹⁰⁴ C. Malettras, B. Decoix, J. Morel, and C. Paulmier, *C. R. Acad. Sci. Ser. C* **276**, 1305 (1973).

¹⁰⁵ C. Malettras, B. Decoix, J. Morel, and P. Pastour, *Bull. Soc. Chim. Fr.*, 1575 (1974).

¹⁰⁶ P. A. Konstantinov, N. M. Koloskova, F. D. Kireeva, and E. M. Malakhaev, *Zh. Obshch. Khim.* **42**, 1780 (1972).



tives were studied and used for the conformational analysis of selenophene-2-aldehyde.¹⁰⁷

Computer simulation of lanthanide-induced shifts in the 2-formyl and 2-acetyl derivatives of furan, thiophene, selenophene, and tellurophene¹⁰⁸ indicate a nearly equipopulated mixture of trans and cis conformers of the furan, and a preponderance of the cis for the thiophene, selenophene, and tellurophene derivatives. This difference is due to an interaction between the ring heteroatom and the carbonyl oxygen lone pair electrons.

Sheinker and co-workers¹⁰⁹ have also investigated the conformations of carbonyl derivatives among the five-membered heterocycles based on the temperature dependence of the dipole moments. However, when the difference between the dipole moments of the two conformations is small, this method becomes ineffective. Other methods based on the Kerr effect¹¹⁰ or calculations by the extended Hückel method and the σ , π method of Dewar point to the very stable X,O-cis form of the heterocyclic aldehydes.¹¹¹ The high stability of the cis form is explained by the fine balance of all the non-bonding interactions in the molecule.¹¹² The observations obtained by different techniques and calculations have also been verified by measurement of the intramolecular nuclear Overhauser effect (NOE).¹¹³ In the series of O-, S-, and Se-containing heterocycles the stabilization of the cis forms increases in the order Se > S > O. The introduction of an electron-withdrawing nitro group leads to a lowering of the potential barrier to internal rotation and facilitates the formation of the trans form. The temperature at which the trans form begins to appear increases on going from the furan to

¹⁰⁷ S. V. Tsukerman, A. I. Yatsenko, V. D. Orlov, and V. F. Lavrushin, *Str. Mol. Kvantovaya Khim.*, 20 (1970).

¹⁰⁸ S. Caccamese, G. Montaudo, A. Recca, F. Fringuelli, and A. Taticchi, *Tetrahedron* **30**, 4129 (1974).

¹⁰⁹ V. N. Sheinker, O. A. Osipov, V. I. Minkin, E. G. Derecha, R. M. Minyaev, V. S. Troilina, A. S. Kuzharov, and N. N. Magdesieva, *Zh. Obshch. Khim.* **44**, 1314 (1974).

¹¹⁰ A. S. Kuzharov, V. N. Sheinker, N. N. Magdesieva, N. A. Koloskova, and O. A. Osipov, *Zh. Obshch. Khim.* **47**, 1671 (1977).

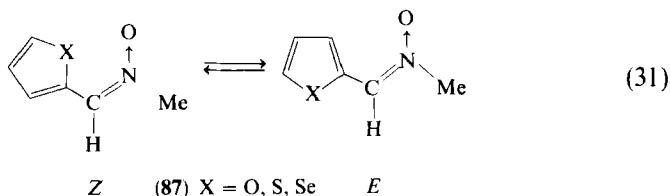
¹¹¹ A. S. Kuzharov, V. N. Sheinker, O. A. Osipov, E. G. Derecha, and N. N. Magdesieva, *Zh. Obshch. Khim.* **45**, 1539 (1975).

¹¹² R. M. Minyaev, V. I. Minkin, and V. N. Sheinker, *Zh. Org. Khim.* **45**, 1950 (1975).

¹¹³ V. N. Sheinker, E. G. Merinova, M. E. Perel'son and O. A. Osipov, *Zh. Obshch. Khim.* **46**, 1582 (1976).

the thiophene and selenophene rings. The introduction of electron-donating groups raises the potential barrier to rotation. Studies concerning the influence of the heteroatom on the conformational equilibrium have also been extended to the tellurophene derivatives.¹¹⁴ The 2-*N,N*-dimethylcarboxamide derivatives of furan, thiophene, and selenophene are found to exist mainly in a quasi-planar *S*-cis form. The barriers to the rotation about the amide bond have been measured and related to the electronegativity of the heteroatom.¹⁰⁸

The conformational equilibria of the aldonitrones (**87**) have been studied.¹¹⁵ The thermodynamically more stable *Z*-form is increasingly



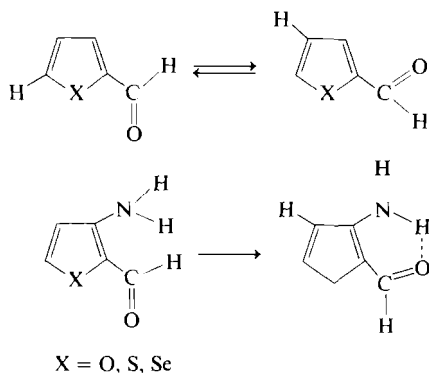
favored over *E* at 20°C on going from the thiophene to the selenophene derivative. However, when the temperature is raised to 90°C, the ratio between the two conformers becomes equal for the two systems. The proportions of the two conformers of the aldonitrones follow the same trend as the carbonyl derivatives on going from furan to selenophene. Because of the increase of the distance between the oxygen in the substituent and the heteroatom in the ring in the aldoximes compared to the carbonyl derivatives, the thermodynamically more stable *Z*-form is however less dominant in the aldoximes.

Substituents such as the amino group in the rings can alter the proportions between *cis* and *trans* conformers in different ways.¹¹⁶ The NMR spectra of such compounds, especially those unsubstituted in the 4- and 5-positions of the ring, can give an estimate of the amount of each conformer present. The long-range couplings between the aldehyde proton and the ring protons are extremely useful. In the *cis* conformation, the aldehyde proton couples with the 5-proton, and in the *trans* conformation with the 4-proton according to the "zig-zag" convention (cf. Scheme 7). In the three heterocycles, furan, thiophene, and selenophene, the 3-amino-2-formyl derivatives show exclusively a long-range coupling to the 4-proton, that is, all exist largely in a *trans* conformation in deuteriochloroform.

¹¹⁴ C. G. Andrieu, D. Debruyne, and Y. Mollier, *C. R. Acad. Sci. Ser. C* **280**, 977 (1975).

¹¹⁵ E. G. Merinova, V. N. Sheinker, O. A. Osipov, and V. I. Piven', *Zh. Obshch. Khim.* **46**, 1191 (1976).

¹¹⁶ S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B29**, 224 (1975).



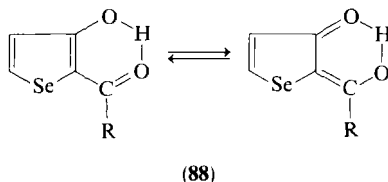
SCHEME 7

X. Hydroxyselenophenes and Their Sulfur and Selenium Analogs

A. PREPARATION AND TAUTOMERIC PROPERTIES

Recently, the hydroxy derivatives of furan, thiophene, and selenophene have been studied with regard to their physical properties and reactions. These compounds are tautomeric and if the oxygen function is placed in the 2-position they exist as unsaturated lactones and undergo carbon-carbon rearrangement, whereas the 3-hydroxy derivatives form oxo-enol tautomeric systems. By NMR the structures of the different tautomeric forms have been determined as well as the position of the tautomeric equilibrium and the rate of isomerization.

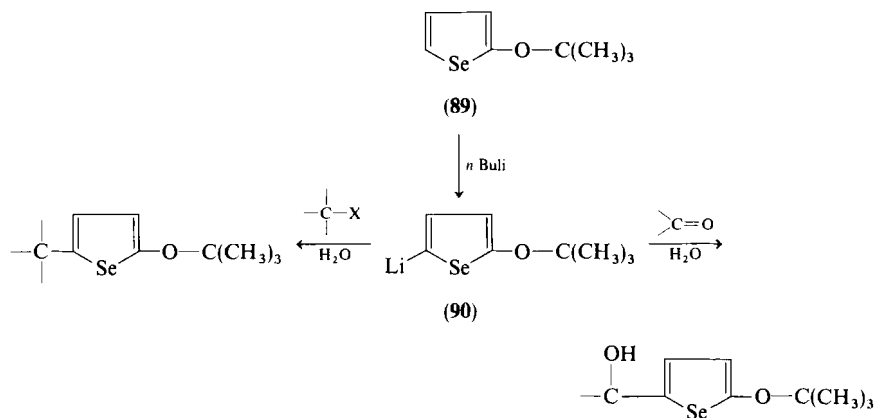
The hydroxy function can be introduced by two methods: by oxidation of selenopheneboronic acids or by dealkylation of *tert*-butylselenophene ethers. Both methods have been used by Pastour and co-workers^{117,118} in their preparation of 2-formyl- and 2-acetyl-3-hydroxyselenophene. The importance of hydrogen bonding for the tautomeric equilibrium (88) is discussed.



¹¹⁷ J. Morel, C. Paulmier, and P. Pastour, *J. Heterocycl. Chem.* **9**, 355 (1972).

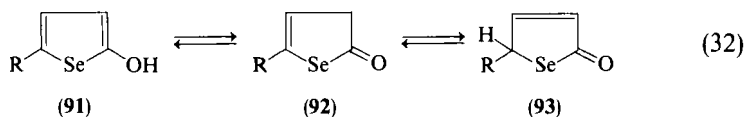
¹¹⁸ C. Paulmier, J. Morel, D. Semard, and P. Pastour, *Bull. Soc. Chim. Fr.*, 2434 (1973).

The 5-lithium derivative (90) obtained upon metalation of 2-*tert*-butyl-selenophene ether (89) was treated either with alkyl halides or with carbonyl derivatives (Scheme 8).



SCHEME 8

This gives tautomeric mixtures¹¹⁹ when the *tert*-butyl group is removed. The methyl ether has been used to obtain 3-hydroxy-2-carbonyl derivatives in the selenophene series.¹²⁰ The unsubstituted 2-hydroxyselenophene system has been prepared by hydrogen peroxide oxidation of 2-selenopheneboronic acid.¹²¹ However, in the 5-methyl-substituted system deboronation became such an important side reaction that 5-methyl-2-hydroxyselenophene had to be prepared by acid-catalyzed dealkylation of 5-methyl-2-*tert*-butoxyselenophene. Both 2-hydroxy- and 5-methyl-2-hydroxyselenophene exist mainly as 3-selenolene-2-ones (93); and for the 5-methyl derivative it was possible to isolate the β,γ -unsaturated form (92) and follow the tautomeric isomerization. The activation parameters thus obtained were compared with those for the corresponding furan and thiophene systems.



2,5-Dimethyl-3-hydroxyselenophene has been prepared by hydrogen peroxide oxidation of the corresponding boronic acids and esters.¹²² The

¹¹⁹ G. Henrio, J. Morel, and P. Pastour, *Ann. Chim. (Paris)* **10**, 37 (1975).

¹²⁰ G. Henrio, J. Morel, and P. Pastour, *Bull. Soc. Chim. Fr.*, 265 (1976).

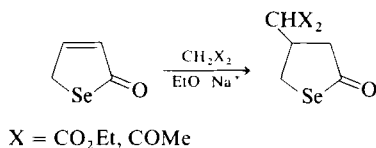
¹²¹ B. Cederlund and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B30**, 101 (1976).

¹²² R. Lantz and A.-B. Hörnfeldt, *Chem. Scr.* **10**, 126 (1976).

enol was characterized as the acetoxyselenophene, and the thermodynamic equilibrium constant was determined by UV spectroscopy and compared with that of the 2,5-dimethyl-3-hydroxythiophene system. The apparent pK_a value for the selenophene was determined by potentiometric titration. The OH acidity was found to be one unit lower than the OH acidity of the analogous thiophene system.

B. REACTIONS

Unsubstituted 2-hydroxyselenophene undergoes Michael addition to its keto tautomer, giving saturated selenolactones (cf. Scheme 9).¹¹⁹

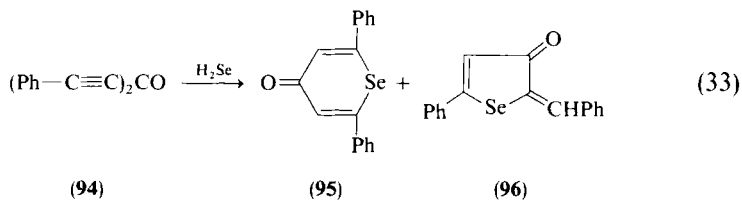


SCHEME 9

Reactions of trident and ambident anions of hydroxy compounds with alkylating reagents were also studied.¹²¹ The ion-pair extraction method was found to be superior; alkylating agents were methyl iodide (soft) and dimethyl sulfate (hard). Upon alkylation by ion-pair extraction the 5-methyl-substituted selenolene-2-one system gives mainly C-alkylation with the soft acid, methyl iodide, and mainly O-alkylation with the hard acid, dimethyl sulfate.

Alkylation of the 2,5-dimethyl-3-hydroxyselenophene system followed the same trend as the 2-hydroxy system: methyl iodide gave predominantly C-alkylation, whereas dimethyl sulfate gave O-alkylation.¹²²

A derivative of the oxo form of a 3-hydroxyselenophene has been obtained by a quite different route.¹²³ 1,5-Diphenyl-1,4-pentadiyn-3-one (**94**) adds hydrogen selenide and gives a mixture of 2,6-diphenyl-1-seleno- γ -pyrone (**95**) and 2-benzylidene-3-oxo-5-phenyl-2,3-dihydroselenophene (**96**).



¹²³ A. I. Tolmachev and M. A. Kudinova, *Khim. Geterotsikl. Soedin.*, 274 (1974).

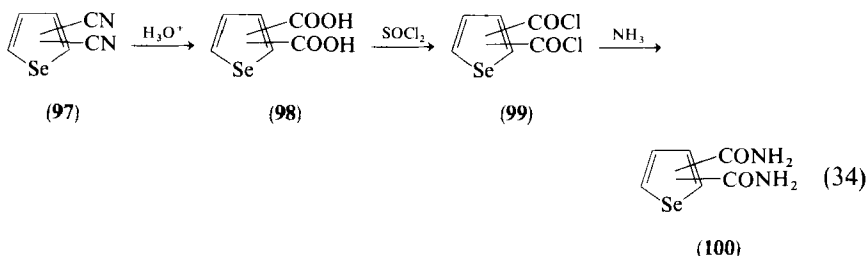
The ionization potentials, using mass spectrometry, for both 2-hydroxy- and 3-hydroxythiophenes have been compared with data for compounds derived from either tautomeric form in order to analyze the tautomeric composition.^{124,125} In the 2-hydroxy-substituted system the enol isomer could not be detected. Of the two possible unsaturated lactones the α,β -unsaturated form was the major isomer. In the 3-hydroxy-substituted case both the oxo form and the enol form are important. The position of the equilibrium was compared with those of the corresponding furan and selenophene systems for both isomers.

The potentially tautomeric side-chain thiol systems exist mainly in the thiol form in liquid solution and in the gas phase, as found by IR and NMR spectroscopy and by a study of ionization potentials.¹²⁶ Upon alkylation using the ion-pair extraction method, only the S-alkylated compounds were obtained. The synthesis, reactions, and properties of some selenides of thiophene, furan, and selenophene have been reviewed.¹²⁷

XI. Selenophenes with Nitrogen-Containing Substituents

A. CYANO DERIVATIVES AND THEIR REACTIONS

Cyano-substituted selenophenes are valuable precursors of formyl derivatives.⁸⁹ They are also used as starting materials for the preparation of carboxylic acids and their derivatives.¹²⁸ By treating the cyano compounds with hydrogen selenide, selenoloamides (**101**) were obtained. As shown in



¹²⁴ O. Thorstad, K. Undheim, B. Cederlund, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B29**, 647 (1975).

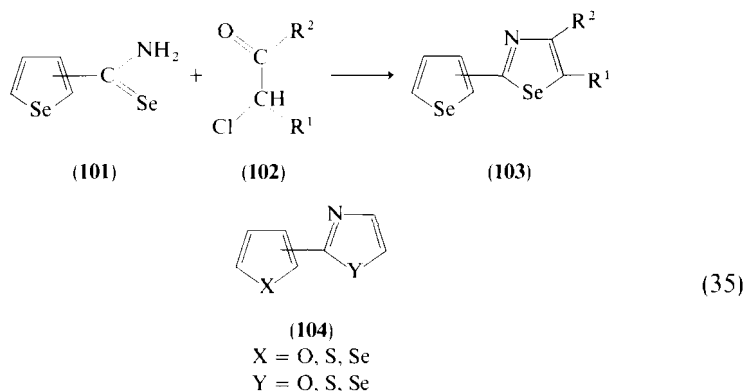
¹²⁵ O. Thorstad, K. Undheim, R. Lantz, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B29**, 652 (1975).

¹²⁶ B. Cederlund, R. Lantz, A.-B. Hörnfeldt, O. Thostad, and K. Undheim, *Acta Chem. Scand., Ser. B* **B31**, 198 (1977).

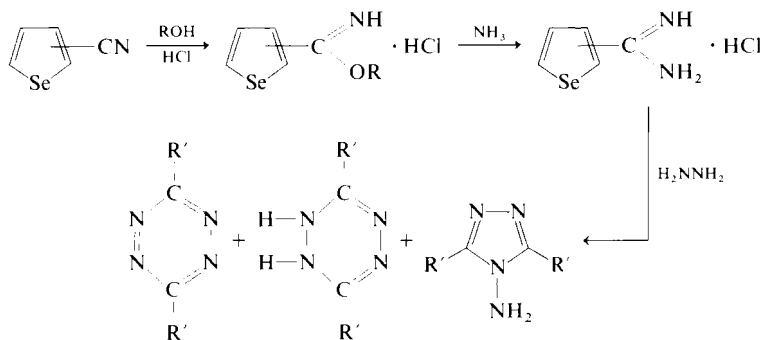
¹²⁷ V. P. Litvinov, A. N. Sukiasyan, and Ya. L. Gol'dfarb, *Usp. Khim. Geterotsikl.*, 186 (1976).

¹²⁸ P. Chauvin, J. Morel, C. Paulmier, and P. Pastour, *C. R. Acad. Sci., Ser. C* **274**, 1347 (1972).

Eq. (35), these compounds give selenienylselenazoles (**103**) upon condensation with α -haloketones (**102**), a reaction that has proven quite general for the preparation of a number of heteroaryl-substituted azoles (**104**).¹²⁹



By reducing dicyanoselenophenes with diisobutylaluminium hydride, cyano, formyl, and diformyl derivatives have been obtained and their reactions with hydrazine and enamines have been studied.¹³⁰ Selenophene-imino ethers, obtained by treating cyanoselenophenes with ethanol and hydrochloric acid, as well as cyanoselenophenes themselves, react with hydrazine to give a variety of polynitrogen compounds.^{131,132} When imino ethers are treated with ammonia, amidines are obtained. Polynitro compounds are formed¹³³ by the reaction of the amidines with hydrazine (cf. Scheme 10).



SCHEME 10

¹²⁹ P. Chauvin, J. Morel, and P. Pastour, *C. R. Acad. Sci., Ser. C* **276**, 1453 (1973).

¹³⁰ P. Dubus, B. Decroix, J. Morel, and P. Pastour, *Bull. Soc. Chim. Fr.*, 628 (1976).

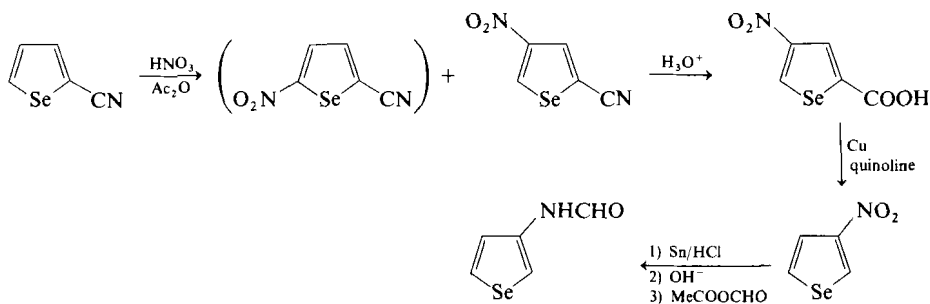
¹³¹ B. Decroix and P. Dubus, *C. R. Acad. Sci., Ser. C* **279**, 343 (1974).

¹³² B. Decroix, P. Dubus, J. Morel, and P. Pastour, *Bull. Soc. Chim. Fr.*, 621 (1976).

¹³³ B. Decroix and P. Pastour, *J. Chem. Res., S.*, 132 (1978).

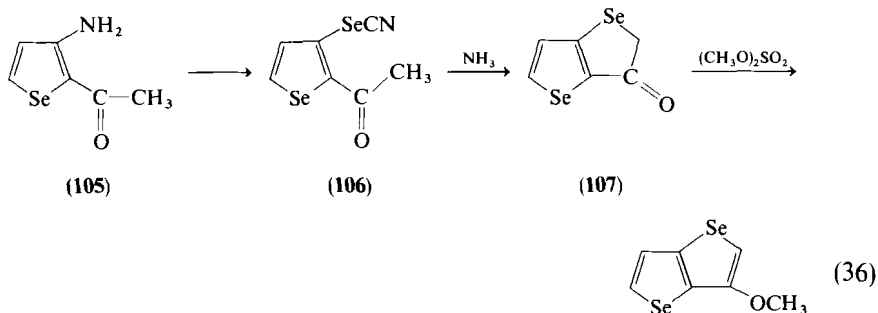
B. AMINO DERIVATIVES AND THEIR REACTIONS

The amino-substituted five-membered heterocycles are unstable compounds, but their acetyl and formyl derivatives can be isolated. *N*-(Selenienyl-3)formamide can be obtained via the reaction route shown in Scheme 11.¹³⁴ An ortho, electron-attracting substituent, such as formyl or nitro, renders amino compounds stable. However, the yield of 2-nitro-3-aminoselenophene is quite low.



SCHEME 11

Diazotization of 3-amino-2-acetylselenophene (**105**) and reaction with potassium selenocyanide yields the selenocyanate (**106**); ring closure with ammonia gives the fused system **107** which was O-methylated with dimethyl-sulfate.¹³⁵



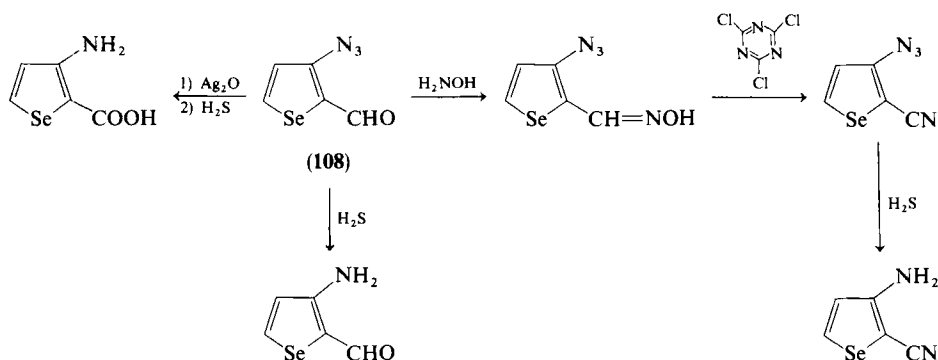
Starting with 3-aminoselenophene, a thiocyno or a selenocyno group could be introduced in the ortho position using ammonium thiocyanate and potassium selenocyanate.^{136,137}

¹³⁴ G. Ah-Kow, C. Paulmier, and P. Pastour, *Bull. Soc. Chim. Fr.*, 151 (1976).

¹³⁵ C. Paulmier, *Bull. Soc. Chim. Fr.*, 237 (1979).

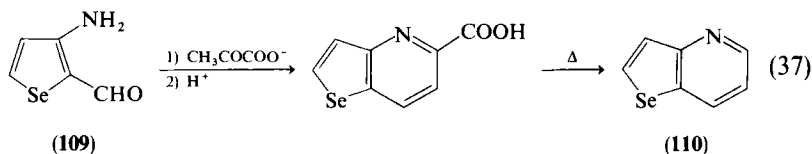
¹³⁶ C. Paulmier, *Bull. Soc. Chim. Fr.*, 592 (1979).

¹³⁷ C. Paulmier, *Tetrahedron Lett.*, 1797 (1978).

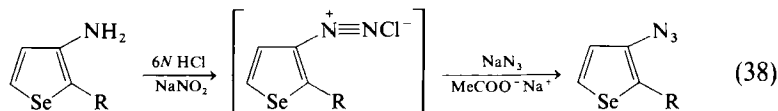


SCHEME 12

A way to introduce the primary amino group directly onto the selenophene ring is via the azido compound, obtained by nucleophilic substitution of the bromo derivative with sodium azide. Useful transformations of the azido group are shown in Scheme 12.¹¹⁷ The amino aldehyde (109) is a suitable starting material for the preparation of selenolo[3,2-*b*]pyridine (110) by the Friedlander reaction.¹³⁸ Not only can the azido be reduced to an amino



group, but it can also be thermally decomposed to give a nitrene. The highly reactive nitrenes can undergo insertion into C—H bonds or addition to unsaturated systems yielding fused heterocyclic compounds as in the preparation of selenolo[3,2-*b*]pyroles¹³⁹ and selenolo[3,2-*c*]isoxazoles.¹⁴⁰ An azido compound was obtained from the amino derivative via the diazonium salt as shown in the preparation of selenolo[3,2-*c*]isoxazole, (Eq. 38).¹⁴¹



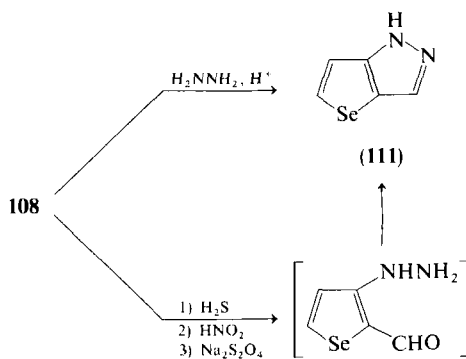
R = CHO, COMe, NO₂

¹³⁸ S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B29**, 233 (1975).

¹³⁹ S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B30**, 391 (1976).

¹⁴⁰ S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Chem. Scr.* **10**, 165 (1976).

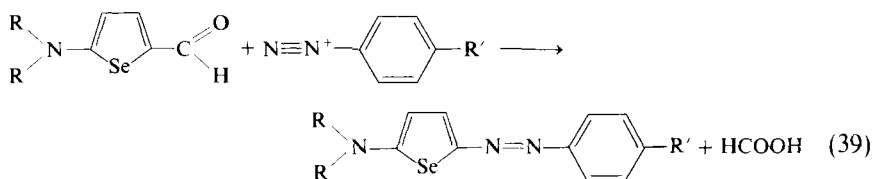
¹⁴¹ C. Paulmier, *C. R. Acad. Sci., Ser. C* **281**, 317 (1975).



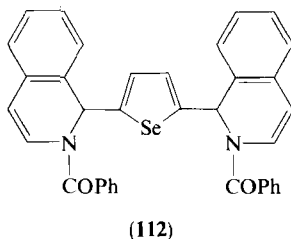
SCHEME 13

A useful method for obtaining indazoles in high yields involves treatment of *ortho*-azido phenyl ketones or aldehydes with hydrazine hydrate. When this reaction was applied to 3-azido-2-formylselenophene, selenolo[3,2-*c*]pyrazole (111) was obtained in low yield. The yield could not be improved when the amino derivative was prepared as an intermediate¹⁴² (Scheme 13).

2-Dialkylamino-5-formylselenophenes react with diazonium salts under deformylation conditions to give azo dyes (Eq. 39).¹⁴³ Another nitrogen-containing derivative of selenophene is compound 112.¹⁴⁴



$R' = NO_2, H, OCH_3$



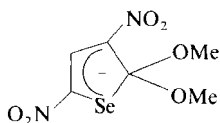
¹⁴² S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Chem. Scr.* **12**, 1 (1977).

¹⁴³ F. A. Mikhailenko and L. I. Shevchuk, *Khim. Geterotsikl. Soedin.*, 1325 (1974).

¹⁴⁴ A. K. Sheinkman, T. V. Stupnikova, and A. A. Deikalo, *Khim. Geterotsikl. Soedin.*, 1147 (1973).

C. MEISENHEIMER COMPLEXES IN THE SELENOPHENE SERIES

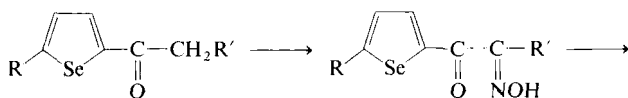
3,5-Dinitro-2-methoxyselenophene gave the first Meisenheimer complex in the selenophene series,¹⁴⁵ (113) which seems to be the most stable *gem*-dimethoxyl adduct yet observed in methanol.¹⁴⁶



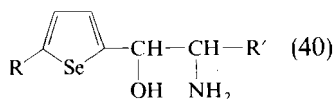
(113)

D. PHARMACOLOGICALLY INTERESTING SELENOPHENES

Because of their interest in physiologically active selenophenes, Magdesieva and co-workers^{147,148} have prepared some α -amino alcohols (115). Ketones (114) were nitrosated and the oximes thus obtained were reduced with lithium aluminium hydride.



(114)



(115)

In order to obtain a compound labeled with a radioactive isotope for studies about the pancreas, β -2- and β -3-selenienyl alanine were prepared. Initially the synthetic route shown in Scheme 14, which allowed insertion of radioactive selenium as late in the synthesis as possible, was designed for the β -2 isomer (116).¹⁴⁹

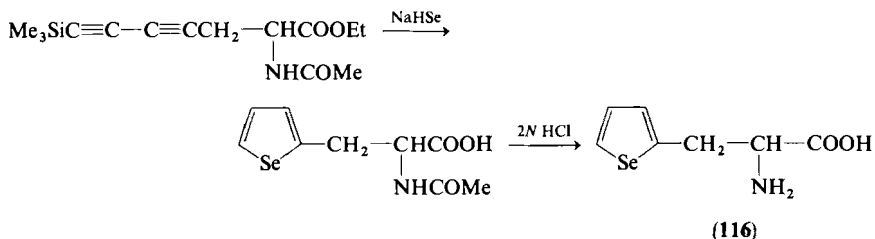
¹⁴⁵ F. Terrier, A.-P. Chatrousse, R. Schaal, C. Paulmier, and P. Pastour, *Tetrahedron Lett.*, 1961 (1972).

¹⁴⁶ F. Terrier, A.-P. Chatrousse, C. Paulmier, and R. Schaal, *J. Org. Chem.* **40**, 2911 (1975).

¹⁴⁷ N. N. Magdesieva and T. A. Balashova, *Khim. Geterotsikl. Soedin.*, 184 (1971).

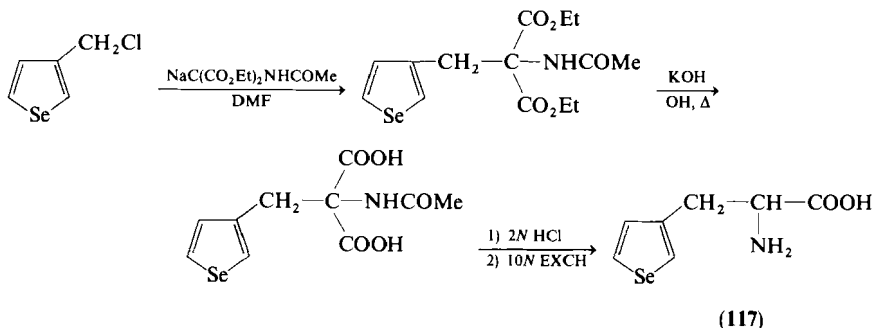
¹⁴⁸ N. N. Magdesieva, T. A. Balashova, and G. M. Dem'yanova, *Khim. Geterotsikl. Soedin.*, 626 (1972).

¹⁴⁹ P. M. Jacobs and M. A. Davis, *J. Org. Chem.* **44**, 178 (1979).



SCHEME 14

The alternative pathway shown in Scheme 15 has the advantage that it is equally suitable for the preparation of *gram* quantities of both the β -2 isomer (116) and the β -3 isomer (117).¹⁵⁰



SCHEME 15

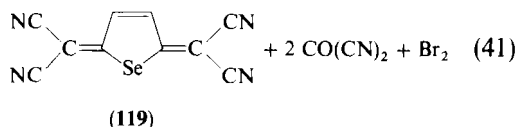
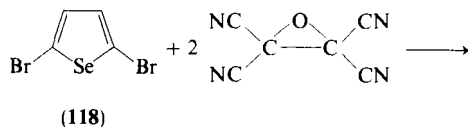
XII. Selenophenes of Potential Technical Utility

The discovery of high conductivity in some organic compounds has initiated a whole era of research. The first and most used acceptor molecule is 7,7,8,8-tetracyanoquinomethane. A selenophene analog has been prepared starting from 2,5-dibromoselenophene (118) as shown in Eq. (41).¹⁵¹ Data for the solution electrochemistry and ESR spectroscopy of 119 and other acceptors containing dicyanomethylene units have been determined.¹⁵² In an attempt to correlate oxidation potentials with LUMO energies no obvious

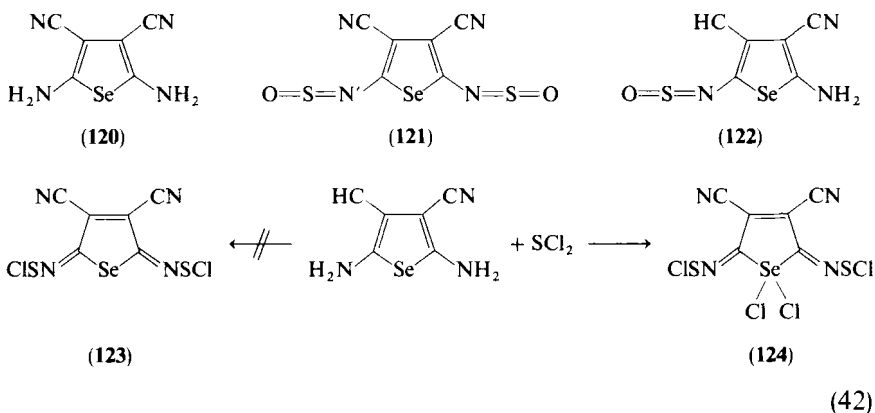
¹⁵⁰ T. Frejd, M. A. Davis, S. Gronowitz, and T. Sadeh, *J. Heterocycl. Chem.* **17**, 759 (1980).

¹⁵¹ S. Gronowitz and B. Uppström, *Acta Chem. Scand., Ser. B* **B28**, 981 (1974).

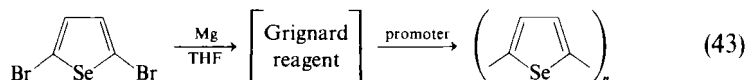
¹⁵² M. L. Kaplan, R. C. Haddon, F. B. Bramwell, F. Wudl, J. H. Marshall, D. O. Cowan, and S. Gronowitz, *J. Phys. Chem.* **84**, 427 (1980).



relationship was found. In addition to donor-acceptor complexes, organic polymers with similarities to the inorganic superconducting polymer $(\text{SN})_x$ have attracted great interest. In order to design such polymers, compounds such as **120**–**122** have been prepared.¹⁵³ In an attempt to prepare **123**, compound **124** was obtained instead.¹⁵⁴ This was somewhat unexpected since the sulfur analog of **123** is known. However, selenium is more electro-positive than sulfur and can expand its valence octet more readily.



Promoted coupling of the Grignard reagent from 2,5-dibromoselenophene affords poly-2-5-selenienylene as shown in Eq. (43). Nickel(II) promoters gave the best results in terms of degree of polymerization and yields.¹⁵⁵



¹⁵³ F. Wudl, E. T. Zellers, and D. Nalewajek, *J. Org. Chem.* **45**, 3211 (1980).

¹⁵⁴ F. Wudl and E. T. Zellers, *J. Am. Chem. Soc.* **102**, 5430 (1980).

¹⁵⁵ M. D. Bezoari, P. Kovacic, S. Gronowitz, and A.-B. Hörnfeldt, accepted for publication.

XIII. Miscellaneous

Electrochemical reduction of 2-formyl- and 2-acetylselenophene has been carried out on a mercury electrode in aqueous ethanol.^{156,157} Cobalt acyclopentadiene complexes are starting materials in the synthesis of 2,5-diphenyl-3,4-dimethylselenophene and 2,5-diphenyl-3,4-selenophenecarboxylic acid dimethyl ester, with good yields.¹⁵⁸ Selenophene has been chloromethylated to 2,5-dichloromethylselenophene, which has been used for the syntheses of other 2,5-substituted derivatives, such as the diacetic acid.¹⁵⁹ 3-Bromomethylselenophene can be prepared from 3-methylselenophene, *N*-bromosuccinimide, and azobisisobutyronitrile in carbon tetrachloride with a reversed addition method.¹⁶⁰ Selenium monocarbonyl ylides have been used in the preparation of 1,2,3-triaroylcyclopropanes containing two and three selenienyl units¹⁶¹ and 2-selenienyl-substituted furans.¹⁶² Condensation of 1,4-dichlorobut-3-en-2-one with malonic esters gives the corresponding Knoevenagel adducts which may be cyclized directly to selenophene-3-malonic esters.¹⁶³ The reactivity of selenophene as a substrate for 2,3-dimethylmaleic anhydride in a benzophenone-photosensitized reaction has been investigated, and the adduct formed showed anti stereochemistry.¹⁶⁴ Another photochemical application is the *cis*-*trans* isomerization of selenienyl analogs of chalcone.¹⁶⁵

¹⁵⁶ D. Guerout and C. Caullet, *C. R. Acad. Sci., Ser. C* **281**, 643 (1975).

¹⁵⁷ D. Guerout and C. Caullet, *C. R. Acad. Sci., Ser. C* **281**, 667 (1975).

¹⁵⁸ Y. Wakatsuki, T. Kuramitsu, and H. Yamazaki, *Tetrahedron Lett.*, 4549 (1974).

¹⁵⁹ M. Y. Kornilov and E. M. Ruban, *Ukr. Khim. Zh.* **35**, 824 (1969).

¹⁶⁰ S. Gronowitz and T. Frejd, *Synth. Commun.* **6**, 475 (1976).

¹⁶¹ N. N. Magdesieva, N. Le Nguyen, and N. M. Koloskova, *Zh. Org. Khim.* **13**, 1010 (1977).

¹⁶² N. N. Magdesieva, N. Le Nguyen, and N. M. Koloskova, *Zh. Org. Khim.* **15**, 609 (1979).

¹⁶³ J. P. Clayton, A. W. Guest, A. W. Taylor, and R. Ramage, *J. C. S. Chem. Commun.*, 500 (1979).

¹⁶⁴ C. Rivas, D. Pacheco, and F. Vargas, *J. Heterocycl. Chem.* **17**, 1151 (1980).

¹⁶⁵ M. Reinhardt, V. G. Mitina, B. A. Zadorozhnyi, and V. F. Lavrushin, *Zh. Obshch. Khim.* **48**, 2759 (1978).

Recent Advances in Furan Chemistry. Part I

FRANCIS M. DEAN

*Department of Organic Chemistry,
University of Liverpool, Liverpool, England*

| | |
|---|-----|
| I. Introduction | 168 |
| II. Syntheses of the Furan Ring | 169 |
| A. From Monosaccharides | 169 |
| B. From Hydrofurans | 169 |
| C. From 1,4-Dicarbonyl Compounds | 172 |
| D. From Feist-Benary Synthesis (Haloketone Reactions) | 174 |
| E. From Epoxides and Glycols | 175 |
| F. From Alkynes | 177 |
| G. From Cumulenes | 179 |
| H. From Cycloaddition Reactions | 182 |
| I. From 1,3-Dicarbonyl Compounds | 185 |
| J. From Butenolides | 187 |
| K. From Pyran and Pyridine Derivatives | 189 |
| L. From Miscellaneous Sources | 190 |
| III. Ionic Attack | 191 |
| A. Electrophiles | 191 |
| B. Protonation | 197 |
| C. Nucleophiles | 200 |
| IV. Lithium, Boron, and Other Elements | 207 |
| A. Metals | 207 |
| 1. Lithium and Potassium | 207 |
| 2. Copper | 211 |
| 3. Tin | 212 |
| 4. Mercury | 213 |
| B. Nonmetals. | 213 |
| 1. Boron | 213 |
| 2. Silicon | 215 |
| 3. Phosphorus | 216 |
| 4. Iodine | 216 |
| V. Radical Chemistry | 216 |
| A. Simple Radicals | 216 |
| B. Carbenes | 223 |
| C. Nitrenes | 225 |
| D. Silylenes | 226 |
| VI. Oxidation and Reduction | 226 |
| A. Electrochemical Processes | 226 |

| | |
|---------------------------------|-----|
| 1. Oxidation | 226 |
| 2. Reduction | 231 |
| B. Chemical Processes | 231 |
| 1. Oxidation | 231 |
| 2. Reduction | 235 |

I. Introduction

This review of furan chemistry is meant to continue the earlier survey by Bosshard and Eugster¹ and concentrates upon the period 1968 to the end of 1979. Like the earlier review, this one is limited to the chemistry of the monocyclic furan nucleus and does not deal, except incidentally, with fused rings such as benzofuran or its quinones. Nor does it deal in detail with dihydro- or tetrahydrofurans, nor with compounds like furylpyridine that contain some other heterocyclic nucleus as well. Some butenolides and tetronic acids are admitted to consideration since they are the carbonyl equivalents of hydroxyfurans regarded as enols, but side-chain reactions are wholly excluded unless the furan nucleus clearly affects them in some important way.

Natural products find a place not as such but at points where, once again, their chemistry illustrates the behavior of their furan nuclei. There are now so many naturally occurring furans (the sea adds its quota to the land plant count every week) that even to make a list, as in the previous review, was too big a task and would have taken too much room; happily, reference to almost any issue of *Phytochemistry* will immediately supply examples and there are already some good lists available elsewhere (eremophilane² and farnesane^{2a} furans, butenolides,³ furanoid fatty acids,⁴ marine products⁵).

Other reviews include a succinct general survey by Sargent and Cresp⁶ and a more detailed one by Soviet authors.⁷ The Soviets have also published a survey of methods for preparing β -substituted furans⁸ as well as a brief

¹ P. Bosshard and C. H. Eugster, *Adv. Heterocycl. Chem.* **7**, 378 (1966).

² A. R. Pinder, *Prog. Chem. Org. Nat. Prod.* **34**, 81 (1977).

^{2a} H. Nikimo and C. Konno, *Heterocycles* **4**, 817 (1976).

³ N. H. Fischer, E. J. Oliver, and H. D. Fischer, *Prog. Chem. Org. Nat. Prod.* **38**, 47 (1979).

⁴ Lei Ken Jie and S. F. Marcel, *Chem. Phys. Lipids* **24**, 407 (1979); C. H. Rahn, D. M. Sand, Y. Wedmid, H. Schlenk, T. P. Krick, and R. L. Glass, *J. Org. Chem.* **44**, 3420 (1979).

⁵ D. J. Faulkner, *Tetrahedron* **33**, 1421 (1977).

⁶ M. V. Sargent and T. M. Cresp, in "Comprehensive Organic Chemistry" (P. G. Sammes, ed.), Vol. 4, p. 693. Pergamon, Oxford, 1979.

⁷ J. Bleidelis, K. Venters, and R. Gevars, "Advances in Furan Chemistry." Zinate; Riga, Latv. SSR, 1978.

⁸ L. D. Krasnoslobodskaya and Ya. L. Gol'dfarb, *Russ. Chem. Rev. (Engl. Transl.)* **38**, 389 (1969).

history of furan compounds.⁹ The lectures presented at an international symposium on furan chemistry have also been published in Russian.¹⁰ Reviews of more specific character are mentioned in the appropriate sections.

II. Syntheses of the Furan Ring

A. FROM MONOSACCHARIDES

The well-known acid-catalyzed conversion of sugars into furan derivatives obviously consists of a complex sequence of reactions, and the industrial heterophasic conversion of pentosans in plant tissues has been discussed in detail.¹¹ The reactions themselves are still not well understood, although xylose and glucuronic acid in deuterium oxide afford 2-furaldehyde without uptake of isotope thus limiting the mechanistic possibilities to those not permitting reversible enolization.¹² The bacterial sugar streptose yields 2-methyl-3-furaldehyde very easily at pH ~ 3 ,¹³ and in the wake of Soviet authors¹⁴ Charon and Szabo have discovered that the transformation of 3-deoxyketoaldonic acids into 5-hydroxyalkyl-2-furoic acids is readily effected even by dilute trifluoroacetic acid at 100°C.¹⁵

A review is available of the synthesis of polyhydroxyalkyl substituted heterocycles, including furans, by condensations of aldose and ketose sugars with β -dicarbonyl compounds.¹⁶

B. FROM HYDROFURANS

The methods discussed are those in which a preexistent hydrofuran ring is converted to a furan ring by eliminating hydrogen or some other species. It also includes some methods not obviously belonging to any other section,

⁹ Ya. P. Z. Stradyn, ed., *Vses. Nauchn. Konf. Khim. Tekhnol. Furanovykh Soedin.* [Tezisy Dokl.], 3rd, 9 (1978) [CA **92**, 127835 (1980)].

¹⁰ J. Kovac, R. Kada, and V. Knoppova, eds., *Collect. Lect.—Int. Symp. Furan Chem.*, 3rd, 1979, (1979).

¹¹ E. P. Morozov, *IUPAC Int. Symp. Chem. Nat. Prod.* **2**, 235 (1978).

¹² M. S. Feather, *Tetrahedron Lett.*, 4143 (1970); H. S. Isbell, *J. Res. Natl. Bur. Stand. (U.S.)* **32**, 45 (1944); E. F. L. J. Anet, *Adv. Carbohydr. Chem.* **19**, 181 (1964).

¹³ K. Tsugi and I. Fujimaki, *Tetrahedron Lett.*, 4229 (1970).

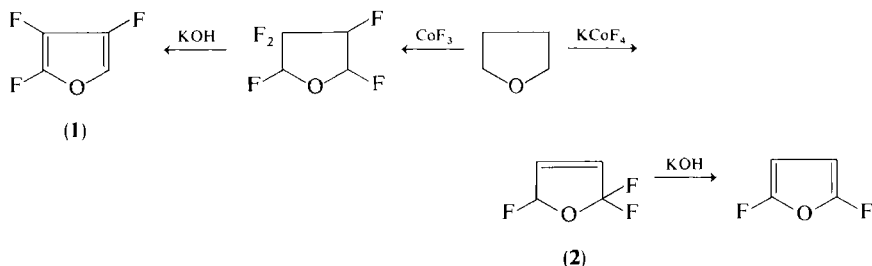
¹⁴ B. A. Dmitriev, L. V. Bakinovskii, and N. K. Kochetkov, *Dokl. Akad. Nauk SSSR* **193**, 1304 (1970).

¹⁵ D. Charon and L. Szabo, *J. C. S. Perkin I*, 1175 (1973).

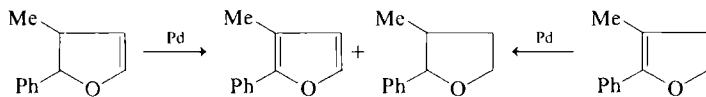
¹⁶ F. Garcia Gonzalez, J. Fernandez-Bdanos, and F. Lopez Aparicio, *ACS Symp. Ser.* **39**, 207 (1976).

in which the ring itself is formed first but with arrangements for eliminations to provide the double bonds later. Such a classification is inevitably unsatisfactory and is only used because the recent proliferation of synthetic methods has blurred the customary demarcations beyond recognition.

As a starting material, tetrahydrofuran has little to recommend it except in rare cases, one of which is the preparation of fluorofurans. With cobalt(III) fluoride, tetrahydrofuran yields a mixture of polyfluoro derivatives from which alkali fusion removes HF leaving various fluorofurans including tetrafluorofuran and 2,3,4-trifluorofuran (1). Potassium tetrafluorocobaltate acts on tetrahydrofuran giving 2 as the main product and alkali fusion converts this into 2,5-difluorofuran. The fluorofurans all polymerize readily and are rather unresponsive to electrophilic reagents.¹⁷



Birch has made good use of oxidative decarboxylation in hydrofuroic acids (Section VI,B,2) but otherwise the direct removal of hydrogen from a hydrofuran is usually regarded as impracticable, and while the dismutation catalyzed by palladium on alumina at 180°C is interesting, it depends too much upon the substitution pattern to be sufficiently general¹⁸:

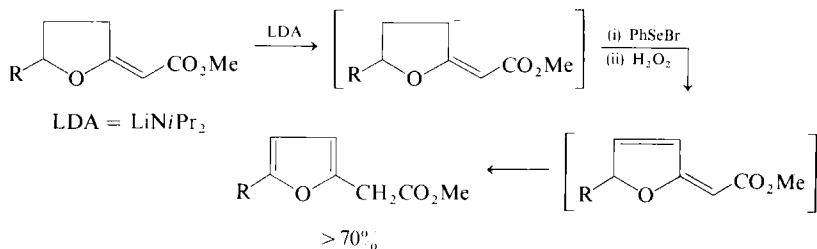


Very simple compounds such as alkyl-substituted tetrahydrofurans can be dehydrogenated by chlorosulfonic acid or by oleum, these reagents having some capacity for oxidation, and furylium ions are produced (Section III,B), but the technique has not been exploited synthetically.¹⁹ The presence of an easily eliminated group helps; indeed, the terpenoid furan solidagenone might well be an artefact formed during isolation from an unstable hydrofuran

¹⁷ J. Burdon, G. E. Chivers, and J. C. Tatlow, *J. Chem. Soc. C*, 2146 (1970).

¹⁸ G. Dana, P. Scribe, and J. P. Girault, *Tetrahedron Lett.*, 4137 (1970).

¹⁹ D. M. Brouwer, J. A. van Doorn, and A. A. Kiffen, *Recl. Trav. Chim. Pays-Bas* **91**, 1359 (1972).



SCHEME I

precursor.²⁰ Another example in the terpenoid area is the elegant transformation of turraeanthin by way of a dihydroxytetrahydrofuran into a β -substituted furan related to gedunin.²¹ A leaving group can be introduced at a late stage as in Scheme 1,²² or provided from the beginning as in many methods.²²⁻³⁰ Of these, two are particularly well adapted to the preparation of 2,3-disubstituted furans,^{23,24} another to 3,4-disubstituted furans,^{23a} one to 2-substituted furans,²⁴ and others to 3-substituted furans.^{8,25} The most common plant furans fall into this last group and have therefore been reviewed separately.⁸ Some have an optically active center near the ring and a synthesis of these has been adapted from the mild decarbonylation of tetrahydrofuran aldehydes.²⁶ Others are 3-acyl- rather than 3-alkylfurans and are usually easily made from 3-furoic acid although cyclization-elimination methods are available.²⁷ The most common elimination is of methanol, largely because of the accessibility of the intermediates either by the methoxylation techniques discussed in Section VI or by methods such as Seyfert's in which an alkyne $\text{HC}\equiv\text{CCH}(\text{OEt})_2$ is condensed with pentanal to give the alcohol $\text{C}_4\text{H}_9\text{CH}(\text{OH})\text{C}\equiv\text{CCH}(\text{OEt})_2$ and subjected to Lindlar semihydrogenation to give $\text{C}_4\text{H}_9\text{CH}(\text{OH})\text{CH}=\text{CHCH}(\text{OEt})_2$ in the *Z*-configuration; this cyclizes merely upon standing and easy acid-catalyzed elimination of ethanol then provides 2-butylfuran.²⁸ Along with these

²⁰ T. Anthonsen, P. H. McCabe, R. McCrindle and R. D. H. Murray, *Tetrahedron* **25**, 2233 (1969).

²¹ J. G. St. C. Buchanan and T. G. Halsall, *J. C. S. Chem. Commun.*, 48 (1969).

²² C. A. Wilson and T. A. Bryson, *J. Org. Chem.*, **40**, 800 (1974).

²³ M. E. Garst and T. A. Spencer, *J. Org. Chem.*, **39**, 584 (1974).

^{23a} M. E. Garst and T. A. Spencer, *J. Am. Chem. Soc.*, **95**, 250 (1973).

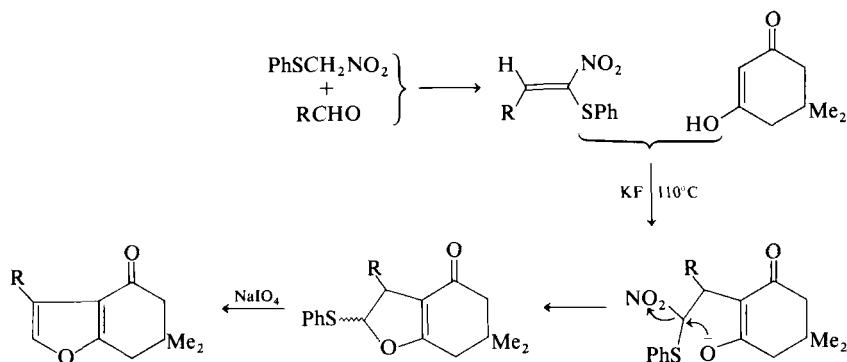
²⁴ H. Kotake and Y. Sakamoto, *Heterocycles*, **10**, 105 (1978).

²⁵ K. Inomata, S. Aoyama, and H. Kotake, *Bull. Chem. Soc. Jpn.*, **51**, 930 (1978).

²⁶ R. Menicaghi, M. L. Wis. L. Lardicci, C. Botteghi, and G. Caccia, *J. C. S. Perkin I*, 847 (1979).

²⁷ K. Inomata, M. Sumita, and H. Kotake, *Chem. Lett.*, 709 (1979).

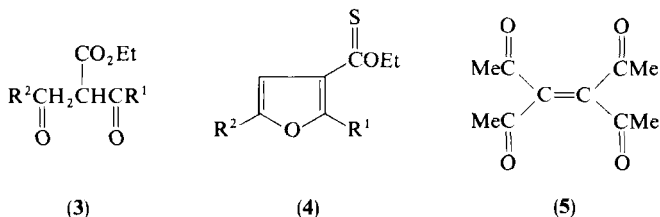
²⁸ H. E. Seyferth, *Chem. Ber.*, **101**, 619 (1968).



ordinary chemical methods there are a few examples of photoeliminations;²⁹ we close, however, with Scheme 2 which shows a route remarkable for the nucleophilic displacement of the nitro group that precedes elimination of benzenethiol to give the furan. This method seems highly adaptable and has been successful in syntheses of evodone and ligularone.³⁰

C. FROM 1,4-DICARBONYL COMPOUNDS

Needing 2,5-dimethylfuran as a masked 1,4-dicarbonyl equivalent, Scott and Naples found that the ion-exchange resin Amberlyst 15 is extremely effective in catalyzing the cyclization of hexane-2,5-dione to this compound.³¹ Some unusual Paal-Knorr reactions have been described. In one, phosphorus(V) sulfide gave none of the expected thiophene when it acted upon the diketoester **3**, the thioester **4** being obtained instead.³² Against all

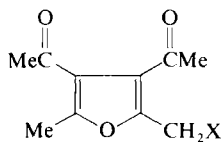


²⁹ S. J. Halkes, A. B. von Etten, T. L. Postmus, J. S. Bontekoe, and M. P. Rappoldt, *Recl. Trav. Chim. Pays-Bas* **98**, 78 (1979).

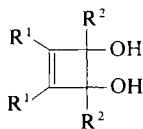
³⁰ M. Miyashita, T. Kumazawa, and A. Yoshikoshi, *J. C. S. Chem. Commun.*, 362 (1978); *Chem. Lett.*, 163 (1979).

³¹ L. T. Scott and J. O. Naples, *Synthesis*, 209 (1973).

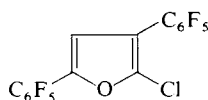
³² C. Trebaul and J. Teste, *Bull. Soc. Chim. Fr.*, 2272 (1970).



(6)

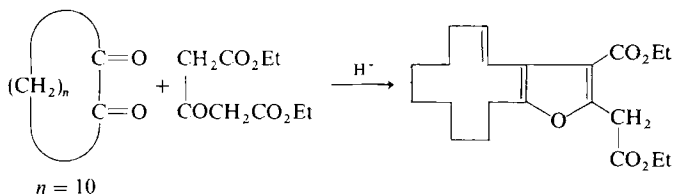


(7)



(8)

appearances, hydrogen halides HX can cyclize the ethylenic tetraketone **5**; a terminal methyl group seems to be enolized for the purpose and halide ion can then add following cyclization to complete the sequence giving **6**.³³ The structure has been confirmed by X-ray analysis.³⁴ A related situation arises in the condensation of cyclic 1,2-diones with acetonedicarboxylic ester, where 4-methylbenzenesulfonic acid is the catalyst and the enolic double bond survives in the product (Scheme 3).³⁵ Another unexpected reaction is induced by 4-methylbenzenesulfonic acid when it converts benzoin into tetraphenylfuran, probably by first catalyzing the disproportionation of benzoin into benzil and deoxybenzoin which later condenses with more benzoin.³⁶



SCHEME 3

It has become common practice to use 1,4-dicarbonyl compounds in various protected forms, especially when one carbonyl group is formyl. An amusing example is the use of cyclobutenediones; with Grignard reagents these readily supply substituted cyclobutenediols **7** which, when heated in xylene, ring-open to 1,4-diketones and then cyclize to furans.³⁷ 2-Substituted acrylic aldehyde acetals react with carbon monoxide and hydrogen under the influence of a rhodium catalyst to give aldehydes $\text{CHOCH}_2\text{CHR}\cdot\text{CH}(\text{OMe})_2$ that with sulfuric acid supply 3-substituted furans in high yields; though this method was devised for the synthesis of furans with optically active centers in R adjacent to the furan ring as in some natural products

³³ G. Adem bri, F. De Sio, R. Nesi, and M. Scotton, *J. Chem. Soc. C*, 1536 (1970).

³⁴ L. Fanfani and P. F. Zanazzi, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* **45**, 158 (1968).

³⁵ O. Campos and J. M. Cook, *J. Heterocycl. Chem.* **14**, 711 (1977).

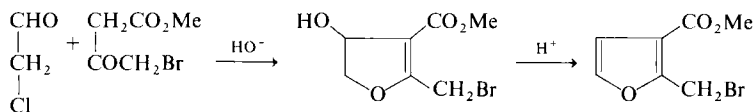
³⁶ S. K. Kar and A. Kar, *J. Org. Chem.* **42**, 390 (1977).

³⁷ J. Hambrecht, *Synthesis*, 280 (1977).

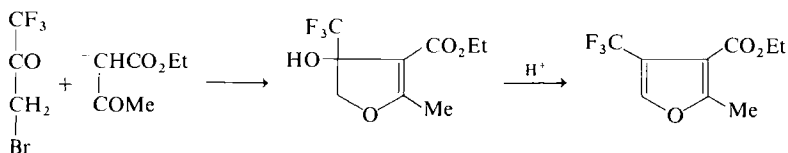
there is some racemization.³⁸ (See also subsection K below.) Another form of carbonyl masking is seen in the methylthioalkenes $\text{MeSC}(\text{R}^2)=\text{CHCH}_2\cdot\text{COR}^1$ which can be smoothly cyclized to 2,5-disubstituted furans by means of titanium(IV) chloride in acetonitrile.³⁹ Orientational problems may be overcome by ketalization of one carbonyl group so as to allow formylation adjacent to an ester function, as when ketonic esters of type $\text{ArCH}_2\text{COCH}_2\cdot\text{CH}_2\text{CO}_2\text{Et}$ are so treated to provide a synthesis of 5-benzyl-3-furoic esters.⁴⁰

D. FROM FEIST-BENARY SYNTHESIS (HALOKETONE REACTIONS)

The Feist-Benary synthesis is still much in evidence, and has been greatly improved for the preparation of 2,3-dimethyl-⁴¹ and other 2,3-disubstituted furans such as ethyl 2-formylfuran-3-carboxylate.⁴² The reaction takes the normal course even in the reaction depicted in Scheme 4, where both components are halogenated carbonyl compounds that could in theory compete with each other.⁴³ The use of fluorinated ketonic esters $\text{F}_3\text{CCOCH}_2\text{CO}_2\text{Et}$ gives the expected 2-trifluoromethylfurans,⁴⁴ and by having the trifluoromethyl group in the other component one obtains a ready synthesis of the isomeric 3-trifluoromethylfurans (Scheme 5).⁴⁵ Although the use in the Feist-Benary method of enamines instead of ketoesters is not uniformly



SCHEME 4



SCHEME 5

³⁸ C. Botteghi, L. Lardicci, and R. Menicagli, *J. Org. Chem.* **38**, 2361 (1973).

³⁹ S. Kano, Y. Tanaka, S. Hibino, and S. Shibuya, *J. C. S. Chem. Commun.*, 238 (1979).

⁴⁰ M. Elliott, N. F. Jones, and B. C. Pearson, *J. Chem. Soc. C*, 2551 (1971).

⁴¹ K. C. Rice and J. R. Dyer, *J. Heterocycl. Chem.* **12**, 1325 (1975).

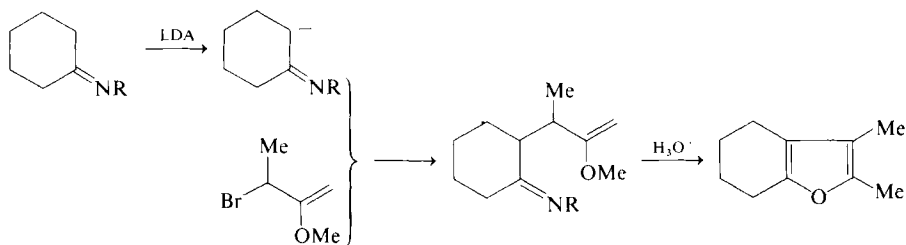
⁴² E. Bisagni, J.-P. Marquat, J.-D. Bourzat, J.-J. Pepin, and J. André-Louisfert, *Bull. Soc. Chim. Fr.*, 4041 (1971).

⁴³ E. Bisagni and C. Rivalle, *Bull. Soc. Chim. Fr.*, 519 (1974).

⁴⁴ R. E. Bambury, H. K. Yarkin, and K. K. Wyckoff, *J. Heterocycl. Chem.* **5**, 95 (1968).

⁴⁵ R. E. Bambury and R. F. Miller, *J. Heterocycl. Chem.* **7**, 269 (1970).

successful⁴⁶ a related idea that combines carbonyl protection/activation as the Schiff base with an electrophilic acetone synthon seems likely to prove helpful (Scheme 6).⁴⁷

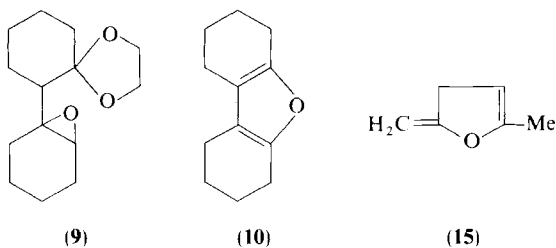


SCHEME 6

The reaction between the copper derivative of pentafluorobenzene and chloroacetyl chloride (ammonia as base) produces a little of the highly stable furan **8**, an unusual result that has been regarded very tentatively as a Feist-Benary reaction with $C_6F_5COCH_2Cl$ as substrate.⁴⁸

E. FROM EPOXIDES AND GLYCOLS

Epoxides (oxirans) and 1,2-diols can also be looked upon as disguised ketones capable of being unmasked by acids. Since its development by Spencer *et al.*⁴⁹ the idea has been utilized by several other groups who used protic acids in work aimed at syntheses of methyl lambertianate,⁵⁰ a rare furanoid fatty acid from an *Exocarpus* species,⁵¹ and a terpenoid furan,



⁴⁶ U. K. Pandit, H. R. Reus, and K. de Jong, *Recl. Trav. Chim. Pays-Bas* **89**, 956 (1970).

⁴⁷ R. M. Jacobson, A. Abbaspour, and G. P. Lahm, *J. Org. Chem.* **42**, 2545 (1977); **43**, 4650 (1978).

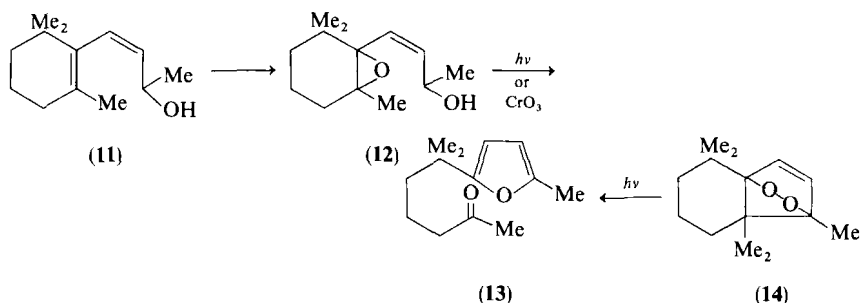
⁴⁸ A. C. Ranade and H. Gilman, *J. Org. Chem.* **6**, 253 (1969).

⁴⁹ T. A. Spencer, R. J. A. Smith, D. L. Storm, and R. M. Villarica, *J. Am. Chem. Soc.* **93**, 4856 (1971).

⁵⁰ R. A. Bell and M. Fétizon, *Can. J. Chem.* **54**, 141 (1976).

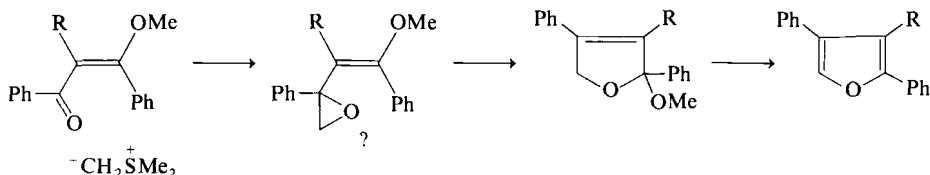
⁵¹ S. Ranganathan, D. Ranganathan, and M. M. Mehrotra, *Synthesis*, 838 (1977).

furanoeremophilone.⁵² Protic acids are probably not the ideal reagents; hence the epoxide-ketal **9**, a doubly protected diketone, is converted into the furan **10** by boron fluoride.⁵³ In the ionone series the peracid oxidation of alcohol **11** yields epoxide **12** whereafter oxidation with chromium(VI) oxide in pyridine immediately leads to the furan **13**, one ring opening as the other closes (Scheme 7).⁵⁴ The ionone epoxide **12** also gives the furan **13**, along with dihydroactinolide and other products, when irradiated at 254 nm.^{55,56} Instead of the epoxide the glycol function suffices⁵⁵ and even the cyclic peroxide **14** gives the same product (**13**) upon irradiation.⁵⁶ In general, however, epoxide routes are not very attractive since they lack specificity unless this can be incorporated in some way.



SCHEME 7

Epoxides are believed to be intermediates in the conversion of the enol ethers of 1,3-diketones (ketoaldehydes are less satisfactory) into 2,4-substituted furans by means of the trimethylsulfonium ylids. No epoxides could be isolated, however, nor was it necessary to use acid to effect cyclization. Methoxydimethylsulfonium ylids were less efficient and tended to produce thiabenzene oxides instead, so Scheme 8 remains speculative.⁵⁷ The use of thioenols instead of 1,3-diones is advantageous.^{2,3a}



SCHEME 8

⁵² T. Sato, M. Toda, and T. Takahashi, *Bull. Chem. Soc. Jpn.* **52**, 3129 (1979).

⁵³ M. W. Creese and E. E. Smismán, *J. Org. Chem.* **41**, 169 (1976).

⁵⁴ B. R. von Wartburg and H. R. Wolf, *Helv. Chim. Acta* **57**, 916 (1974).

⁵⁵ B. R. von Wartburg, H. R. Wolf, and O. Jeger, *Helv. Chim. Acta* **56**, 1948 (1973).

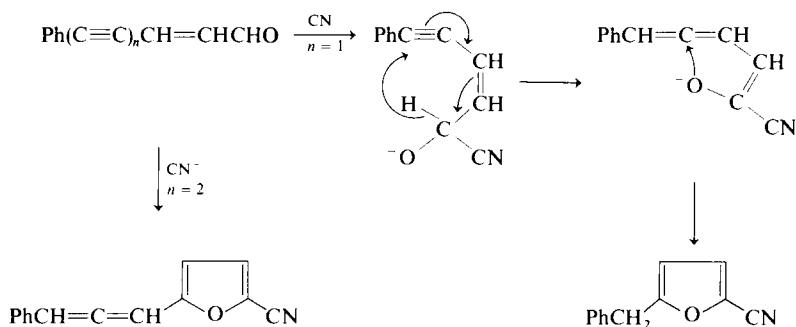
⁵⁶ W. Skorjanetz and G. Ohloff, *Helv. Chim. Acta* **56**, 2151 (1973).

⁵⁷ C. M. Harris, J. J. Cleary, and T. M. Harris, *J. Org. Chem.* **39**, 72 (1974).

Epoxides figure in yet other routes,^{58,59} while even the simple dehydration of ketonic glycols is still valuable.⁶⁰ Epoxides and glycols also figure in routes based upon acetylene chemistry, to which we now proceed.

F. FROM ALKYNES

The acetylenic link can also be regarded as a carbonyl equivalent, and again, methods using it give mixtures unless a control feature is provided. Thus the cyclization of skipped diynes with boron trifluoride or mercury-catalyzed reaction with perchloric acid does yield furans, but only in admixture with other products.⁶¹ Simpler situations can be created by having the latent furan oxygen atom correctly placed within the molecule initially. In hex-4-yne-2-one, base-catalyzed enolization is followed by cyclization giving the exomethylene furan **15** which then aromatizes to 2,5-dimethylfuran.⁶² The oxygen atom in ethynyloxirans provides the furan oxygen atom under the influence of mercury and acid catalysts^{62a} but attempts to combine acetoacetate and acetylene methodologies seem to lead to too complex a situation although it is possible to obtain furylcumulenes as one type of product.⁶³ Furylcumulenes are also obtainable (along with their acetylenic isomers) by an extension of a furan synthesis devised by Bonnet and Bohlmann⁶⁴ who invoke hydride transfer to a cyanohydrin to explain how cyanide ion in excess transforms ene-yne-als into aralkylfurans and the corresponding diynes into the cumulenes (Scheme 9).



SCHEME 9

⁵⁸ D. L. Dare, I. D. Entwistle, and R. A. W. Johnstone, *J. C. S. Perkin I*, 1130 (1973).

⁵⁹ J. C. Trisler, J. K. Doty, and J. M. Robinson, *J. Org. Chem.* **34**, 3421 (1969).

⁶⁰ K. W. Gopinath, P. K. Mahanta, F. Bohlmann, and C. Zdero, *Tetrahedron* **32**, 737 (1976).

⁶¹ W. J. Gensler, J.-C. Petitpierre, and J. W. Dean, *J. Org. Chem.* **43**, 4081 (1978).

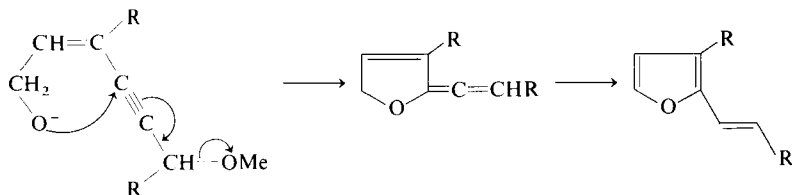
⁶² A. Doutheau and J. Gore, *Bull. Soc. Chim. Fr.*, 2047 (1976).

^{62a} A. Doutheau and J. Gore, *Tetrahedron* **32**, 2705 (1976).

⁶³ D. Miller, *J. Chem. Soc. C*, 12, 1969.

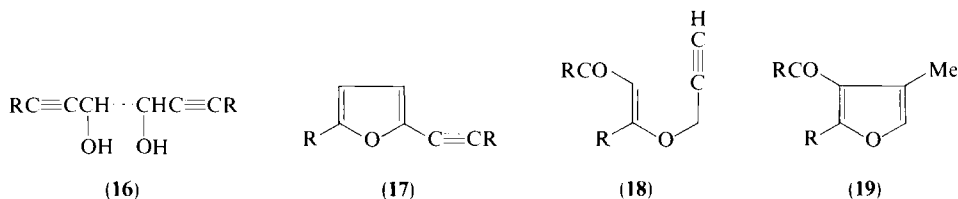
⁶⁴ P.-H. Bonnet and F. Bohlmann, *Chem. Ber* **104**, 1616 (1971).

Simple acetylenic allylic alcohols can be cyclized easily by *tert*-butoxide, and since this base initiates prototropic shifts the vinylic link may be *E* or *Z*; such cyclizations proceed via exomethylene furans similar to **15**.⁶⁵ If necessary, UV irradiation can effect both the isomerization of an *E* to a *Z*-alkene and the cyclization, leaving only the final adjustments to be made chemically.⁶⁶ In a variation, methoxide plays the role of leaving group allowing very good yields to be attained (Scheme 10).⁶⁷



SCHEME 10

Provided they have the meso configuration, symmetrical diacetylenic glycols **16** also cyclize readily in alkali giving high yields of acetylenic furans **17** if R is aromatic; if R is aliphatic the reaction stops at an intermediate dihydrofuranol which has to be dehydrated in a separate step.⁶⁸ Acetylenic glycols can also be efficiently cyclized to furans by means of mercury(II) chloride,⁶⁹ or by bistrisphenylphosphinepalladium salts, diacetylenic glycols yielding acetylenic furans **17**.⁷⁰



Several syntheses of furans are based upon the use of acetylenes to form carbon-carbon linkages. Of two that employ palladium catalysts,^{71,72} one is outlined in Scheme 11.⁷¹ A simpler approach is to treat a 1,3-diketone with

⁶⁵ P. H. M. Schreurs, W. G. Galesloot, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **94**, 706 (1975).

⁶⁶ F. Böhlmann and W. Skuballa, *Chem. Ber.* **104**, 1962 (1971).

⁶⁷ A. J. de Jong, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **93**, 15 (1974).

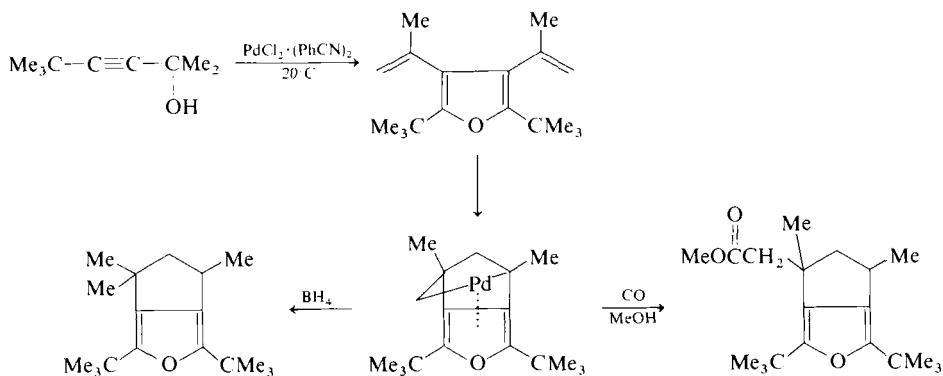
⁶⁸ S. Holand and R. Epsztein, *Bull. Soc. Chim. Fr.*, 1694 (1971).

⁶⁹ S. Galaj, Y. Guichon, and Y.-L. Pascal, *C. R. Acad. Sci., Ser. C* **288**, 541 (1979).

⁷⁰ A. Fabrycy and Z. Wichert, *Zh. Obshch. Khim.* **49**, 2499 (1979).

⁷¹ W. Munzemaier and H. Straub, *Justus Liebig's Ann. Chem.*, 313 (1977).

⁷² M. Avram, E. Avram, F. Chiraleu, E. Sliam, and C. D. Nenitzescu, *Chem. Ber.* **108**, 1830 (1975).



SCHEME 11

a propynyl halide and cyclize the resulting enol ether **18** with mercury catalysts to form a 3-acylfuran (**19**).^{73,74} Carbon-carbon bond formation is also induced by light when benzoylacetylene is mixed with an aliphatic alcohol and irradiated to produce a 2-alkyl-5-phenylfuran.⁷⁵ A special case of great interest is the reaction of di-*N*-ethyl-1-propynamine with acyloins to give derivatives of 2,2':3',2''-trifuran⁷⁶ (see also Section H).

G. FROM CUMULENES

Since cumulenes and alkynes are often easily interconvertible, many syntheses discussed above have allenic counterparts, especially base-catalyzed cyclizations of allenic alcohols.⁷⁷ And, of course, several of the alkyne-based syntheses may well have allenic intermediates. There are, however, a few syntheses based specifically upon allene chemistry. In an important one, due to Stirling and his collaborators,⁷⁸ an allenic sulfonium salt reacts with an enolate anion. Scheme 12 sketches the main features; yields as high as 86% are recorded. Methoxyallene is easily metallated by butyllithium and so converted into an allenic epoxide that can be isomerized by *tert*-butoxide into a furan (Scheme 13) or an exocyclic equivalent similar to **15**; clearly this method is particularly suited to the preparation of 3-methoxyfuran

⁷³ M. Yamamoto, *J. C. S. Perkin I*, 3161 (1979).

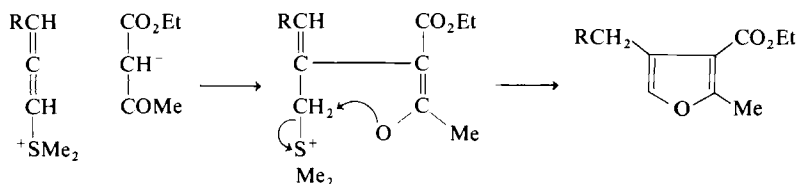
⁷⁴ K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm. (Weinheim, Ger.)* **295**, 62 (1962).

⁷⁵ T. Nishio and Y. Omoto, *J. C. S. Perkin I*, 1703 (1979).

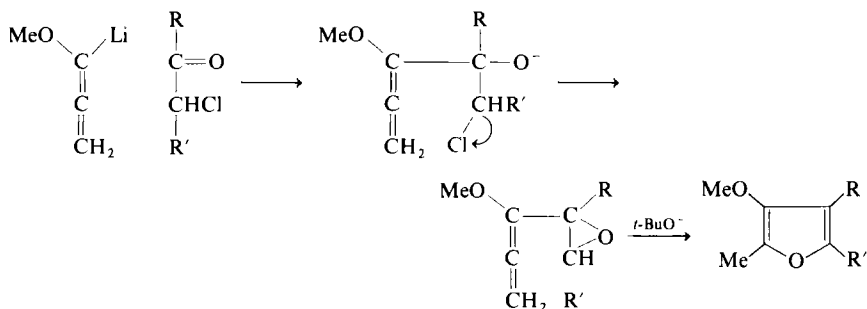
⁷⁶ S. Pennanen, *Heterocycles* **6**, 701 (1977).

⁷⁷ J. A. Rompes, S. Hoff, P. P. Montijn, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **88**, 1445 (1969).

⁷⁸ J. W. Batty, P. D. Howes, and C. J. Stirling, *J. C. S. Perkin I*, 65 (1973).



SCHEME 12



SCHEME 13

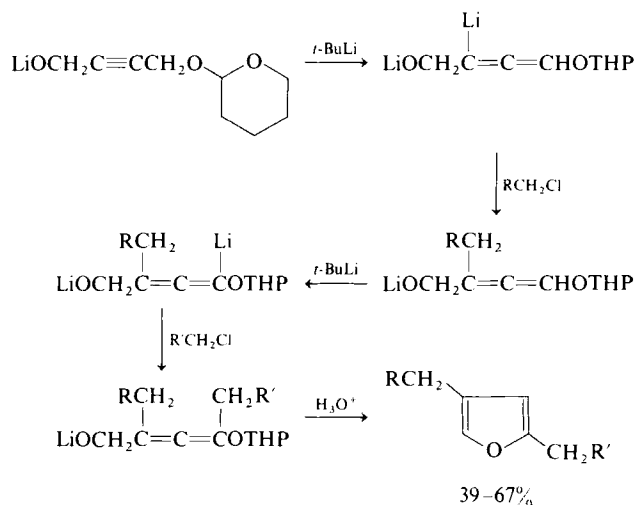
derivatives.⁷⁹ A noteworthy use of metallation occurs in a furan synthesis devised by Staehle and Schlosser who, beginning with 2-butyne-1,4-diol, protect one hydroxy group with a tetrahydropyranyl residue, lithiate the other hydroxy group and then using sequential treatments with *tert*-butyllithium produce an allenic system into which two (different) alkyl residues are introduced before cyclization to a 2,4-disubstituted furan (Scheme 14).⁸⁰ A variation provides 2,3,5-trisubstituted furans.

Dipropynyl ethers offer excellent opportunities for the synthesis of furans because they already contain the oxygen atom along with the right degree of unsaturation. Cyclization is effected with strong bases, and the products show a considerable diversity controlled by the nature of the terminal substituents. Three are illustrated in Scheme 15. Isomerization to the cumulene is always the first step. After that, terminal alkyl groups allow for a proton removal leading to 3-vinylfuran derivatives (**20**) not previously available (Route A).⁸¹ If there are no reactive terminal substituents the cumulene cyclizes to form a bisallylic radical that can either dimerize (if R = H) giving a cyclooctabisfuran (**21**) or cyclize internally once again (if R = *t*-Bu) giving the 3-oxabicyclo[3.2.0]hepta-1,3-diene **22** (Route B).

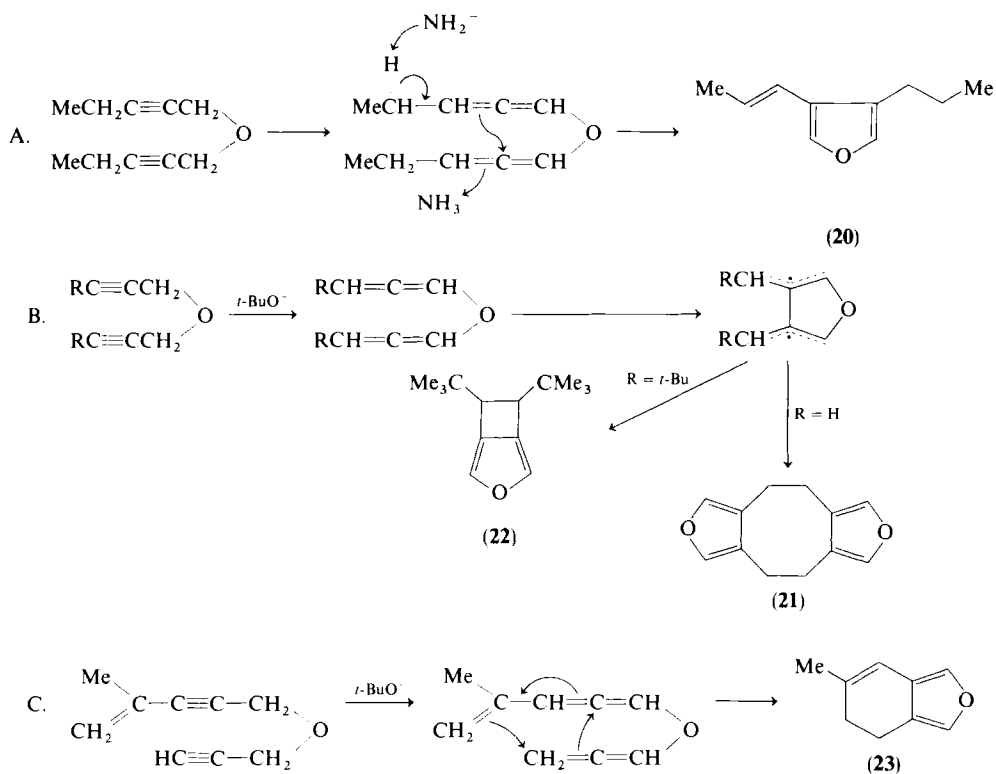
⁷⁹ P. H. M. Schreurs, J. Meijer, P. Vermeer, and L. Brandsma, *Tetrahedron Lett.*, 2387 (1976).

⁸⁰ M. Staehle and M. Schlosser, *Angew. Chem.* **91**, 938 (1979).

⁸¹ P. P. Montijn, A. Kupecz, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **88**, 958 (1969).



SCHEME 14

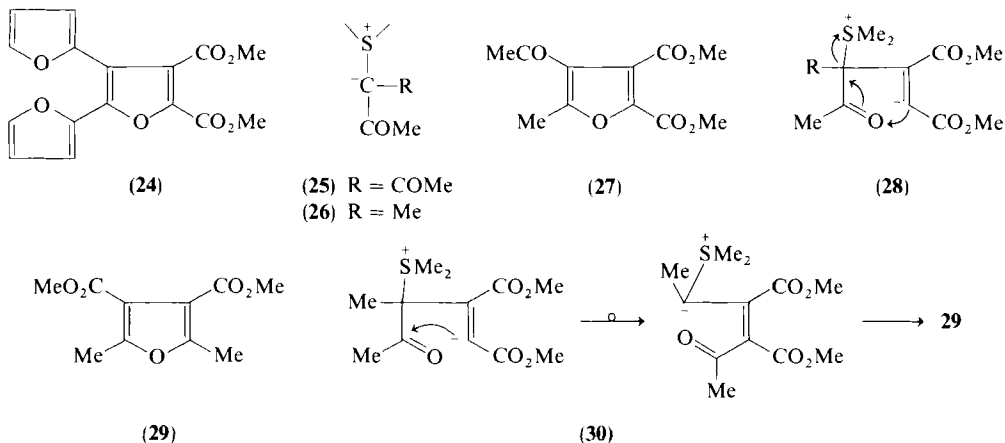


SCHEME 15

The biradical can also effect redistribution (if $R = \text{Ph}$) leading to a naphthalenofuran derivative (not shown).⁸² Should the terminal group be vinylic, the intermediate cumulene can effect a $[2 + 4]$ internal cycloaddition shown in Route C, giving the isobenzofuran derivative **23**.⁸³

H. FROM CYCLOADDITION REACTIONS

Methyl acetylenedicarboxylate (MAD; methyl butynedioate) continues to find many uses in furan chemistry. Its addition to compounds like benzoin is base-catalyzed and offers a good route to 2,3-diarylfurans⁸⁴; applied to furoin it gives the unusual compound **24**.⁸⁵ (Compare Ref. 76). In such reactions the substrate behaves as an enolate anion rather than as a simple alkoxide, and water is eliminated in the aromatization step. Some schools have made use of the superior leaving-group abilities of sulfonium sulfur. Diacylmethylides of type **25** react at temperatures up to 170°C to give acylated furans (**27**), perhaps via the interesting cyclization depicted in **28**.⁸⁶ In dimethyl sulfoxide, on the other hand, reaction proceeds at ordinary temperatures but acyl migrations may intervene. Thus ylid **26** is



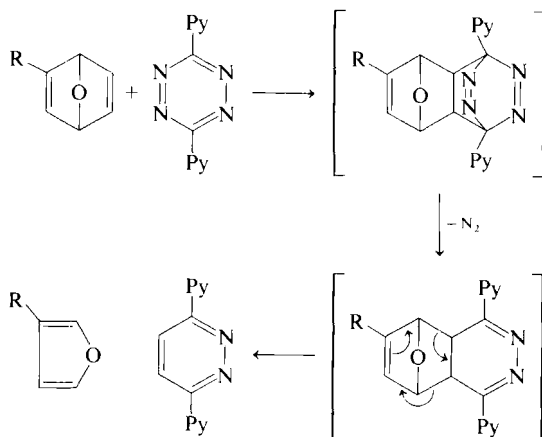
⁸² P. J. Garratt and Soon Bin Neoh, *J. Org. Chem.* **44**, 2667 (1979).

⁸³ A. J. Bartlett, T. Laird, and W. D. Ollis, *J. C. S. Chem. Commun.*, 496 (1974).

⁸⁴ D. T. Anderson and W. M. Horspool, *J. C. S. Perkin I*, 352 (1972).

⁸⁵ S. Pennanen, *J. Heterocycl. Chem.* **14**, 745 (1977).

⁸⁶ M. Takaku, Y. Hayasi, and H. Nozaki, *Tetrahedron Lett.*, 2053 (1969); Y. Hayasi, M. Kobayasi, and H. Nozaki, *Tetrahedron* **26**, 4353 (1970).



SCHEME 16

attacked to give the 3,4-dicarboxylate **29** where the 2,3-isomer might again have been expected; the acyl migration shown in **30** is likely to be responsible since the immediate rearrangement product can be isolated before it cyclizes to the furan.⁸⁷ The method has been extended to the preparation of 5-methylfuran-2,3,4-tricarboxylic acid,⁸⁸ and modified by the use of selenium instead of sulfur ylids.⁸⁹

Some new kinds of cycloaddition-fragmentation reactions have been described in the synthesis of furans; as in the original Alder-Rickert synthesis, all require an alkyne, usually methyl acetylenedicarboxylate. Wilson and Warrener⁹⁰ have evolved a method of conducting the fragmentation stage efficiently at ordinary temperatures. Once formed, the cycloaddition product (a 7-oxanorbornadiene) is allowed to add to a disubstituted 1,2,4,5-tetrazine whereupon nitrogen is eliminated immediately followed by a 1,2-diazine (Scheme 16). Both fragmentations are highly favorable energetically, and the conversions approach the quantitative. Ohlson and Turner⁹¹ point out that, in Scheme 17 leading from **31** via **32** to **33**, X and Y can be CH in which case hydrogenation is needed and the fragmentation has to extrude an alkene which is neither very convenient nor particularly efficient. Where X = Y = N, on the other hand, elimination should be easy since nitrogen can be ejected at once, but the oxadiazoles do not add alkynes

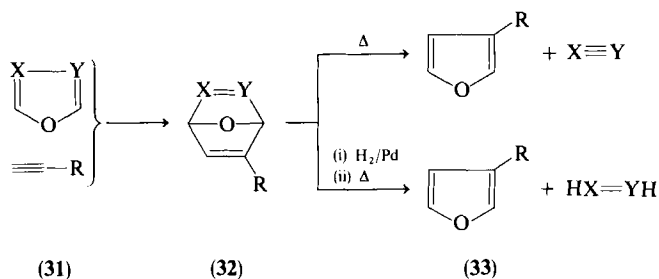
⁸⁷ M. Higo and T. Mukaiyama, *Tetrahedron Lett.*, 2565 (1970).

⁸⁸ H. Saiachi and T. Kitagawa, *Chem. Pharm. Bull.*, **25**, 809 (1977).

⁸⁹ N. N. Magdesieva, Le Nguyen Nghi, and N. M. Koloskova, *Zh. Org. Khim.*, **15**, 609 (1979).

⁹⁰ W. S. Wilson and R. N. Warrener, *J. C. S. Chem. Commun.*, 211 (1972).

⁹¹ S. R. Ohlson and S. Turner, *J. Chem. Soc. C*, 1632 (1971).



SCHEME 17

readily. However, when $\text{X} = \text{CPh}$ and $\text{Y} = \text{N}$ the addition of alkyne to the oxazole (31; $\text{X} = \text{N}$; $\text{Y} = \text{CPh}$) is easy, and the extrusion of benzonitrile is smooth at 115°C thus giving fair yields of 3-acylfurans (including 3-furoic acid) from the appropriate acylated alkyne.⁹¹ The method is now in wide use and provides a good preparation of a useful starting material for furan studies, i.e., furan-3,4-bismethanol.⁹² Ethoxyoxazoles add alkyne esters well and since the ethoxy group in a 2-ethoxy oxazole eventually appears at the 2-position of the furan the method also constitutes a butenolide synthesis.⁹³ Unfortunately, arylalkynes do not add well, some not at all.⁹³ 4-Methyloxazole-5-carbonitrile adds a variety of alkynes to give substituted furan-2-carbonitriles; two isomers are possible in theory but only one is formed in quantity as MO calculations predict.⁹⁴ Since oxazol-4(5H)-ones are tautomeric 4-hydroxyoxazoles, 2-phenyl derivatives (34) allow a synthesis of 2-phenylfurancarboxylic acids.⁹⁵ An internal addition of alkyne to ethoxyoxazole can be observed in 35 and forms the key step in a synthesis of furan derivative 36 which has been generalized with the eventual synthesis of oxygenated sesquiterpenes in mind.⁹⁶ Other possibilities in this area include cycloadditions to mesoionic 1,3-oxathiol-4-enes giving adducts of type 37 that lose carbon oxysulfide to give the substituted furans,⁹⁷ and the use of mesionic systems to facilitate just the fragmentation step in much the same way as the tetrazine above.⁹⁸

⁹² J. Hutton, B. Potts, and P. F. Southern, *Synth. Commun.* **9**, 789 (1979).

⁹³ H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.* **92**, 4340 (1970); R. Grigg and J. L. Jackson, *J. Chem. Soc. C*, 552 (1970); L. B. Medvedskaya, G. Ya. Kondrat'eva, and N. V. Bykanova, *Izv. Akad. Nauk SSSR*, 1613 (1979); J. J. K. Novac, *Collect. Czech. Chem. Commun.* **40**, 2855 (1975); T. Jaworski and T. Mizerski, *Rocz. Chem.* **50**, 359 (1976).

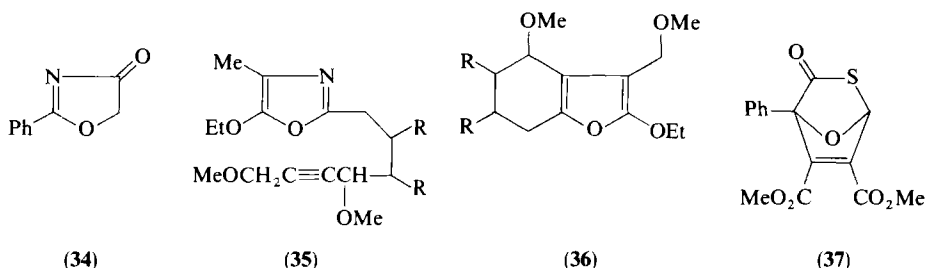
⁹⁴ T. Jaworski, T. Mizerski, and A. Krolikowska, *Pol. J. Chem.* **53**, 1799 (1979).

⁹⁵ K. T. Potts and J. Marshall, *J. C. S. Chem. Commun.*, 1000 (1972).

⁹⁶ P. A. Jacobi and T. Craig, *J. Am. Chem. Soc.* **100**, 7748 (1978).

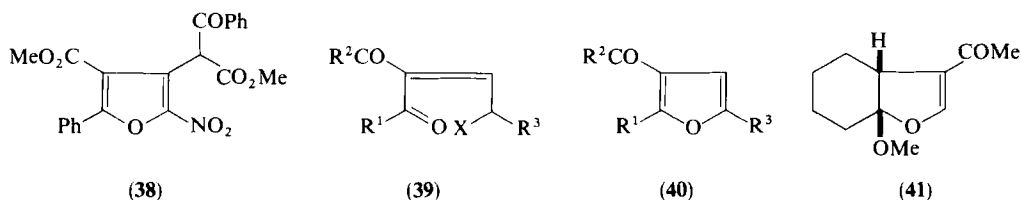
⁹⁷ H. Gotthardt, C. M. Weissshuhn, and K. Dörhöfer, *Chem. Ber.* **111**, 3336 (1979).

⁹⁸ H. Matsukubo and H. Kato, *J. C. S. Chem. Commun.*, 840 (1975).



I. FROM 1,3-DICARBONYL COMPOUNDS

1,3-Dicarbonyl compounds can be converted into furans by methods other than the classical Feist-Benary method, the essential feature of which is alkylation by a haloketone or similar species. A curious variation is provided by the use of trichloronitroethene, $\text{Cl}_2\text{C}=\text{CCINO}_2$, which condenses with two moles of a 1,3-dicarbonyl compound by Michael addition followed by elimination of two chloride ions; the third chloride is lost at the aromatization step so that, for example, methyl 3-oxobenzenepropanoate is converted into the nitrofuran **38**.⁹⁹



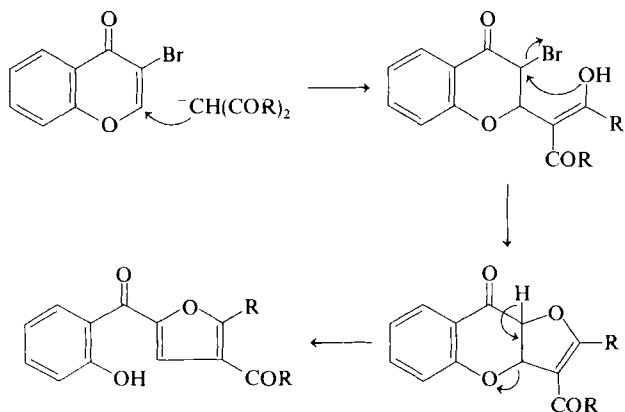
Chromones are also Michael acceptors, and Scheme 18 shows how 3-bromochromone reacts with 1,3-diketones in basic media. The reaction is fairly general and the yields can be as high as 90%, moreover, phenolic furans are not common and the approach provides an effective way of protecting the phenolic hydroxy group during furan ring formation.¹⁰⁰

Aldehydes can be condensed with 1,3-diketones to give vinylic diketones **39** ($\text{X} = \text{H}$) and *N*-bromsuccinimide converts these into the bromides **39** ($\text{X} = \text{Br}$) which supply furans **40** when heated. Yields are poor if the product carries no 5-substituent.¹⁰¹

⁹⁹ L. I. Deiko, V. A. Buevich, V. S. Grimeva, and V. V. Perekalin, *Khim. Geterotsikl. Soedin.*, 1148 (1975).

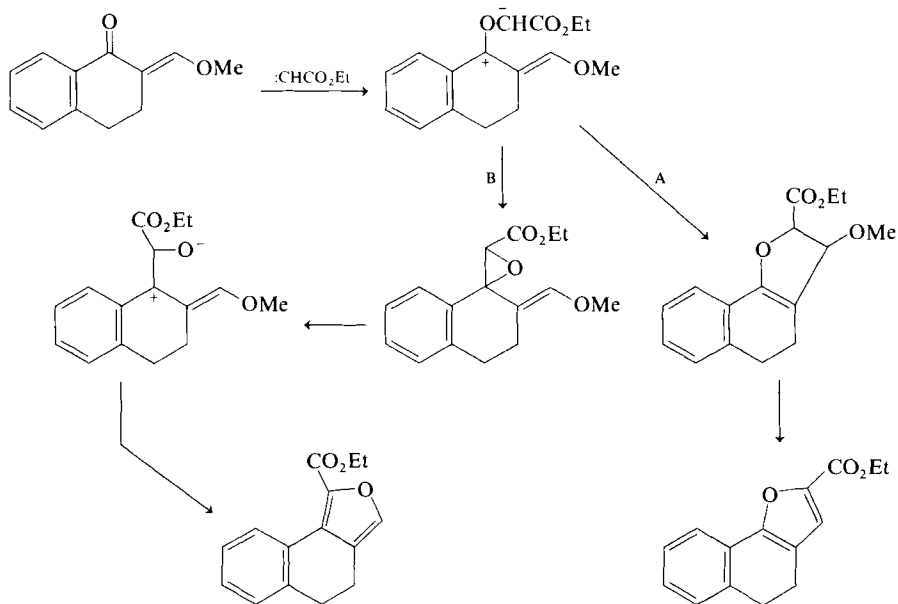
¹⁰⁰ R. B. Gammill, *J. Org. Chem.* **44**, 3988 (1979).

¹⁰¹ R. A. Kretchmer and R. A. Laitar, *J. Org. Chem.* **43** 4596 (1978).



SCHEME 18

Quite different methods employ carbene intermediates. Spencer and his colleagues generate a carbenoid species from ethyl diazoacetate (CuSO_4 catalyst) and allow it to attack an enol ether of a 1,3-diketone.¹⁰² Scheme



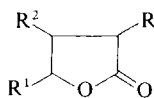
SCHEME 19

¹⁰² D. L. Storm and T. A. Spencer, *Tetrahedron Lett.*, 1865 (1967); S. T. Murayama and T. A. Spencer, *ibid.*, 4479 (1969).

19 shows two routes, A and B, are possible and both may occur; commonly, however, only route A is important, as in a synthesis of the natural furan methyl vinylatocate.¹⁰³ Rhodium and palladium catalysts are said to be much better than the usual copper catalysts because they induce reaction at ordinary temperatures and are more specific, the orientation corresponding to route A in Scheme 19.¹⁰⁴ Simple diazoketones decompose in vinyl ethers to give cyclopropane derivatives, but 2-diazo-1,3-diketones often supply furan derivatives as in the conversion of 1-methoxycyclohexene into the dihydrofuran **41**. For many variations consult Wenkert and co-workers.¹⁰⁵

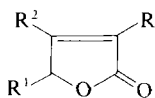
J. FROM BUTENOLIDES

Since reduction plus elimination reactions may convert butenolides into furans, any butenolide synthesis can be a basis for a furan synthesis. Typically, a starting lactone (**42**) treated with lithium diisopropylamide forms the enolate anion, alkylation of which gives **43**: this point can be reached alternatively by treating a 2-exomethylenelactone with an organo-copper reagent. Treatment with strong base followed by phenylselenium bromide, and then hydrogen peroxide, leads to the butenolide **44**, after which reduction to the ketal by diisopropylaluminum hydride and elimination of water provides the furan **45**.¹⁰⁶ Since many naturally occurring furans are terpenoid, the use of terpene acids is appropriate. With strong base methyl geranate affords an anion, oxidation of which supplies the necessary alcohol **46**: the benzoate ester cyclizes to a butenolide that is reduced by metal hydride to furan **47**, isomeric with another important terpene rosefuran (**48**). Dendrolasin has been obtained similarly.¹⁰⁷

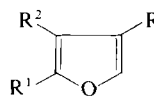


(42) R = H

(43) R = alkyl



(44)



(45)

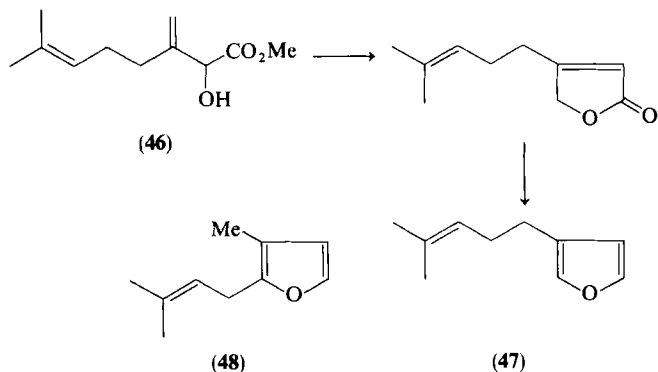
¹⁰³ T. A. Spencer, R. M. Villarica, D. L. Storm, T. D. Weaver, R. J. Friary, J. Posler, and P. R. Shafer, *J. Am. Chem. Soc.* **89**, 5497 (1967).

¹⁰⁴ R. Paulissen, E. Hayez, A. J. Hubert, and P. Teyssie, *Tetrahedron Lett.*, 607 (1974).

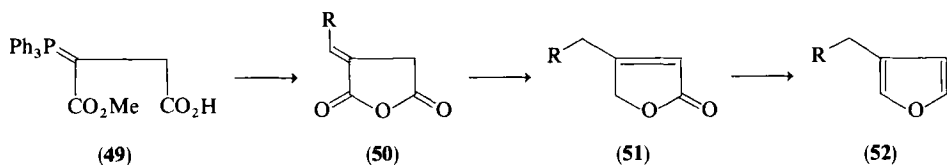
¹⁰⁵ E. Wenkert, M. E. Alonso, B. L. Buckwalter, and K. J. Chou, *J. Am. Chem. Soc.* **99**, 4778 (1977).

¹⁰⁶ P. A. Grieco, C. S. Pogonowski, and S. Burke, *J. Org. Chem.* **40**, 542 (1975).

¹⁰⁷ S. Katsumura, A. Ohsuka, and M. Kotake, *Heterocycles* **10**, 87 (1978).



Californian workers use a slightly different approach (Scheme 20) involving phosphorus ylid **49** (obtained by adding triphenylphosphine to maleic anhydride and treating with methanol) to provide the furan ring. The ylid in Wittig reactions with aldehydes affords exomethylene anhydrides (**50**) that are reduced to exomethylene lactones by means of sodium diethylhydroaluminate and then isomerized to butenolides (**51**) by acid.¹⁰⁸ Reduction to furan **52** is effected by diisobutylaluminum hydride at -40°C —the most popular reagent used also for syntheses of isodrimenin¹⁰⁹ and lindrestrene.¹¹⁰ Gedge and Pattenden describe related syntheses of rosefuran (**48**) and of sesquirosefuran from butenolide precursors with accent on the problem of regioselective prenylation.¹¹¹



SCHEME 20

An unusual rearrangement of a 3-hydroxymethyl-4-hydroxybutenolide into a furan-3-carboxylic acid occurs in the natural product, photogedunin, when it is treated with alkali; the reaction is really related to some of those in sub-sections B, C, and E.^{111a}

¹⁰⁸ J. E. McMurry and S. F. Donovan, *Tetrahedron Lett.*, 2869 (1977).

¹⁰⁹ W. Akita, T. Naito, and T. Oishi, *Chem. Lett.*, 1365 (1979).

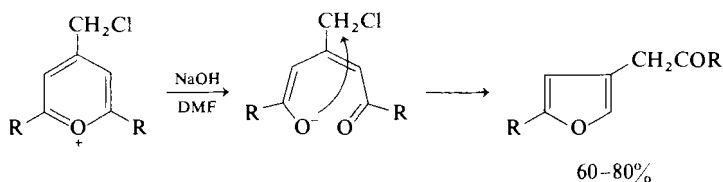
¹¹⁰ H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 621 (1968).

¹¹¹ D. R. Gedge and G. Pattenden, *Tetrahedron Lett.*, 4443 (1977).

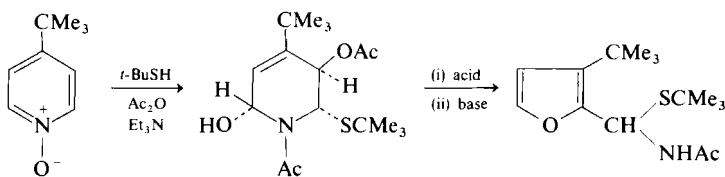
^{111a} B. A. Burke, W. R. Chan, K. E. Magnus, and D. R. Taylor, *Tetrahedron* **25**, 5007 (1969).

K. FROM PYRAN AND PYRIDINE DERIVATIVES

Ring contractions of pyran derivatives are occasionally valuable. The contraction of 3-halo-2-pyrones to 2-furoic acids under the influence of alkali has been studied and the conditions defined.^{58,112,113} The method is adaptable to the preparation of 3-furoic acid via furan-2,4-dicarboxylic acid⁵⁸ and of 3,4,5-triphenylfuran-2-carboxylic acid.¹¹³ Another ring contraction involving halides is the conversion of 4-chloromethylpyrylium salts into furylmethyl ketones as indicated in Scheme 21.¹¹⁴ Pyridine oxides may be transformed with unexpected ease into furans through treatment with a thiol (Scheme 22).¹¹⁵



SCHEME 21



SCHEME 22

Increasing use is being made of pyran syntheses based upon $[4 + 2]$ cycloadditions of carbonyl compounds. The appropriate unsaturated aldehyde with ethyl vinyl ether yields **53**; with peracids this affords an epoxide that undergoes ring contraction to the aldehyde **54** (Scheme 23) and rhodium catalyzed decarbonylation affords the required 3-alkylfuran with the optical center intact.¹¹⁶ Acetoxybutadiene derivatives add active carbonyl compounds giving pyrans that contract under the influence of acids to give

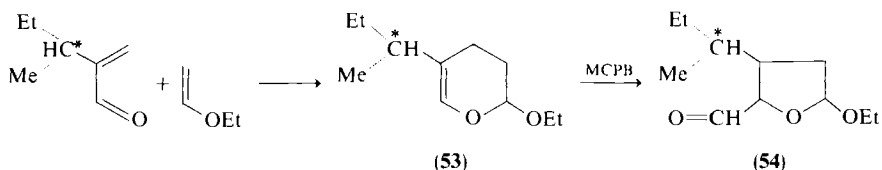
¹¹² T. L. Gilchrist and C. W. Rees, *J. Chem. Soc. C*, 769 (1968).

¹¹³ I. E. El-Kholy, M. M. Mishrikey, and H. M. Fuid-Alla, *J. Heterocycl. Chem.* **12**, 129 (1975).

¹¹⁴ V. I. Dulenko, N. N. Alekseer, V. M. Golyak, and L. V. Dulenko, *Khim. Geterotsikl. Soedin.*, 1135 (1977).

¹¹⁵ J. M. Kokosa, I. Chua, L. Bauer, and R. S. Egan, *J. Heterocycl. Chem.* **13**, 861 (1976).

¹¹⁶ R. Menicagli, M. L. Wis, L. Lardicci, C. Botteghi, and G. Caccia, *J. C. S. Perkin I*, 847 (1979).



SCHEME 23

furans without the need for an epoxidation step.¹¹⁷ Photochemical techniques are discussed in Section VII.

L. FROM MISCELLANEOUS SOURCES

The Claisen (hetero-Cope) rearrangement of tropolone allyl ethers provides entry into the furotropone series¹¹⁸ and is probably adaptable, whereas two routes to tetrakis(trifluoromethyl)furan are highly specialized^{119,120} and probably owe something to the stabilization that might be expected from a combination of electron-rich furan nuclei with electron-attracting substituents, furan **8** having particular thermal stability.⁴⁸

The most direct of all furan syntheses is enshrined in a patent;¹²¹ an appropriately alkyl substituted butadiene is catalytically oxidized to the furan in the presence of copper compounds and iodine. Butadienes can also combine with singlet oxygen to give cyclic peroxides which, in the presence of FeSO_4 are thought to collapse via radical anions as shown in Scheme 24. This method is a good general source of 3-alkylfurans, applicable in the terpene field to syntheses of perillaketone, α -clausenane, ipomeamarone, drendrolasin and torreyal among other natural furans.¹²² It has also been used in biomimetic transformations of unsaturated fatty acids into furans, and a fine example occurs in the destruction by air in sunlight of the butadiene-derived sex pheromone of the female Egyptian cotton leafworm.¹²³ UV irradiation acts similarly on such epidioxides.⁵⁶

¹¹⁷ J. F. W. Keana and P. E. Eckler, *J. Org. Chem.* **41**, 2850 (1976).

¹¹⁸ H. Takeshita, K. Tarjiri, and I. Kouno, *Heterocycles* **6**, 1101 (1977); *Bull. Chem. Soc. Jpn.* **52**, 223 (1979).

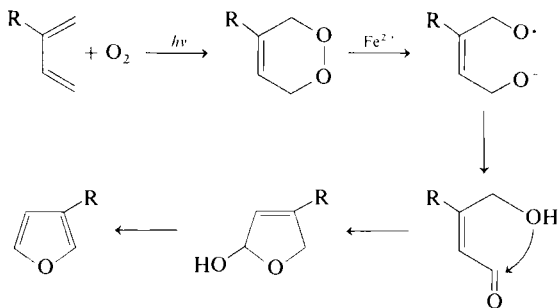
¹¹⁹ Y. Kobayashi, Y. Hanzawa, Y. Nakanishi, and T. Kashiwagi *Tetrahedron Lett.*, 1019 (1978).

¹²⁰ C. J. Boriack, E. D. Laganis, and D. M. Lemal, *Tetrahedron Lett.*, 1015 (1978).

¹²¹ D. L. Garnett and M. L. Peterson, U.S. Patent 4,172,838 [*CA* **92**, 58200 (1980)].

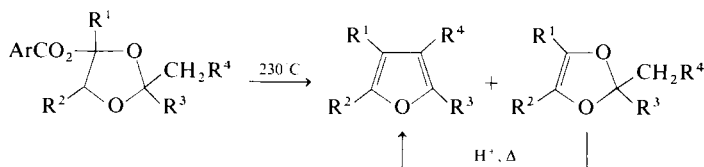
¹²² J. A. Turner and W. Herz, *J. Org. Chem.* **42**, 1900 (1977); K. Kondo and M. Matsumoto, *Tetrahedron Lett.*, 391, 4363 (1976); *Chem. Lett.*, 701 (1974).

¹²³ F. D. Gunstone and R. C. Wijesundera, *Chem. Phys. Lipids* **24**, 193 (1979); A. Shani and J. T. Klug, *Tetrahedron Lett.* **21**, 1563 (1980).



SCHEME 24

Finally, Scharf and Wolters report a method said to be superior to both the Paal-Knorr synthesis (starting materials more easily accessible) and the Feist-Benary synthesis (freer choice for 3-substituent). Thermal rearrangement-elimination by alkylated dioxolanes at $230^\circ C$ gives alkyl substituted furans. Yields can be nearly quantitative since the only serious by-products also give the furans under proton-catalyzed thermolysis (Scheme 25).¹²⁴ Photochemical methods are outlined in Section VII.



SCHEME 25

III. Ionic Attack

A. ELECTROPHILES

Extensive synthetic use continues to be made of electrophilic substitution reactions, as previously summarized by Bosshard and Eugster,¹ especially in combination with lithiations. For typical details the reader can consult papers by several French groups,¹²⁵ by Davis and Loughheed,¹²⁶ by Kutney,

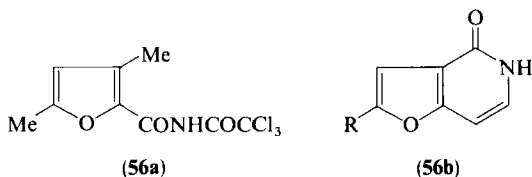
¹²⁴ H.-D Scharf and E. Wolters, *Angew. Chem., Int. Ed. Engl.* **15**, 682 (1976).

¹²⁵ B. Decroix, J. Morel, C. Paulmier, and P. Pastour, *Bull. Soc. Chim. Fr.*, 1848 (1972); M.-C. Zoluski, M. Robba, and M. Bonhomme, *ibid.*, 1838 (1979); R. Sornay, J.-M. Meunier, and P. Fournari, *ibid.*, 990 (1971).

¹²⁶ C. S. Davis and G. S. Loughheed, *J. Heterocycl. Chem.* **4**, 153 (1967).

Hanssen, and Nair,¹²⁷ and by Chadwick *et al.*¹²⁸ All deal with mono-, di-, tri-, and sometimes tetra-substituted furans where the substituents are variously selected from halogen, ester, acid, aldehyde, and ketonic functions. Here we consider only some more special situations.

The ease with which furans react with electrophiles is forcibly demonstrated by the reaction (in CHCl_3 at 25°C) of 2,4-dimethylfuran with trichloroacetyl isocyanate to give the amide **56a**.¹²⁹ Attack at the 3-position is not easy, but still the azide of 3-(2-furyl)propenoic acid at 230°C gives an isocyanate that



spontaneously cyclizes to the lactam **56b** in a reaction for which an electrocyclic mechanism can also be written.¹³⁰ New reagents and techniques have been introduced so that electrophilic substitution may be effected under the mildest, least acidic conditions possible. Furans can be allylated,¹³¹ benzylated,¹³² or acetylated¹³³ in the 2-position by the appropriate 4-methylbenzenesulfonates; lithium perchlorate serves as catalyst for the alkylations.¹³¹ Some authors¹³³ employ allylic halides in liquid SO_2 at -50°C with silver acetate to promote carbenium ion formation and note that such reactions might really proceed by way of cycloadditions (Section VIII,D,3); this interplay of substitution and addition reactions is one of the fascinating features of furan chemistry that is constantly present and frequently poses unsolved problems. An example is a reaction with ethanedithiol under the influence of boron chloride.¹³⁴ 2-Furylmethanol merely alkylates one thiol group giving a 2-furylmethylthioether; furan-2-carboxaldehyde gives the expected dithiolan (thioketal), while furan itself, benzofuran, and some alkylfurans add the thiol to the ring double bonds (Scheme 26).

¹²⁷ J. P. Kutney, H. W. Hanssen, and C. V. Nair, *Tetrahedron* **27**, 3323 (1971).

¹²⁸ D. J. Chadwick, J. Chambers, H. E. Hargreaves, G. D. Meakins, and R. L. Snowden, *J. C. S. Perkin I*, 2327 (1973); D. J. Chadwick, J. Chambers, P. K. G. Hodgson, G. D. Meakins, and R. L. Snowden, *ibid.*, 1141 (1974); D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *ibid.*, 1766 (1973).

¹²⁹ Z. Samek and L. Novotny, *Tetrahedron Lett.*, 5167 (1972).

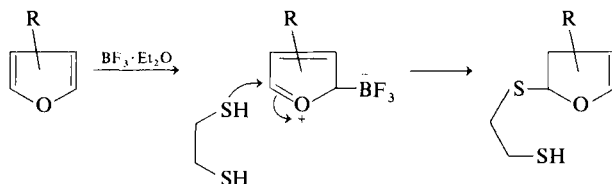
¹³⁰ F. Eloy and A. Deryckere, *J. Heterocycl. Chem.* **8**, 57 (1971).

¹³¹ P. H. Boyle, J. H. Coy, and H. N. Dobbs, *J. C. S. Perkin I*, 1617 (1972).

¹³² S. Pennanen, *Heterocycles* **4**, 1021 (1976).

¹³³ H. M. R. Hoffmann and N. P. Janes, *J. Chem. Soc. C*, 1456, (1969); *J. Chem. Soc. B*, 57 (1968).

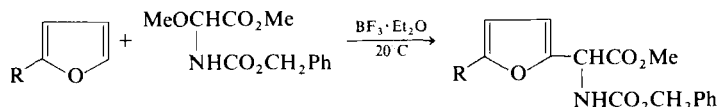
¹³⁴ B. Rindone and C. Scholastico, *J. Chem. Soc. C*, 3339 (1971).



SCHEME 26

Furans are even reactive enough to be substituted by some diazonium salts or diazopyrazoles, though other reactions are usual (Section V,A),¹³⁵ and catalysts are used in response to difficulty in producing an electrophilic species not because the furan ring is unreactive. Scheme 27 shows the synthesis of an interesting α -amino acid derivative¹³⁶ by electrophilic substitution.

Nitration of furfuryl alcohol (2-furylmethanol) in acetic anhydride yields the nitro-nitrate **57** which possesses both a reactive methylene group able to undergo aldol reactions, etc., and also a nitrate ion leaving group for nucleophilic substitutions.¹³⁷ Detailed studies of the nitration disclose various products resulting from the addition of one or even two acetic acid residues to the furan nucleus in competition with the nitrations.^{138,139}



SCHEME 27

Generally, electrophilic attack at the 3(4)-position is negligible unless both 2(5)-positions are filled or unless it is otherwise forced, as in a cyclization.¹⁴⁰ Probably very small amounts of 3(4)-substitution occur and are overlooked in ordinary work though they can be found, if sought carefully, even in nitrations.¹⁴¹ Ciranni and Clementi¹⁴² discuss this matter (the α/β ratio) in

¹³⁵ M. G. Bartle, S. T. Gore, R. K. Mackie, S. Mhatie, and J. M. Tedder, *J. C. S. Perkin I*, 401 (1978); M. Kocevar, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.* **18**, 1175 (1978).

¹³⁶ D. Ben-Ishai, I. Sataty, and Z. Bernstein, *Tetrahedron* **32**, 1571 (1976).

¹³⁷ A. Jurasek, J. Kovac, A. Krutosikova, and M. Hrdina, *Collect. Czech. Chem. Commun.* **37**, 3144 (1972); A. Krutosikova, V. Konecny, and J. Kovac, *ibid.* **40**, 2529 (1975); I. Sroková, A. Jurasek, M. Dandarova, and J. Kovac, *ibid.* **43**, 463 (1978); R. Kada, V. Knoppova, J. Kovac, and A. Jurasek, *ibid.*, 156; K. Venters, M. Trusul, and S. Hillers, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 230 (1977); 284 (1976).

¹³⁸ R. A. Vazquez, J. Fernandez Jimenez, and R. Maestro Duran, *An. Quim.* **72**, 910 (1976).

¹³⁹ D. Lola, K. Venters, E. Liepins, M. Trusul, and S. Hillers, *Khim. Geterotsikl. Soedin.*, 601 (1976).

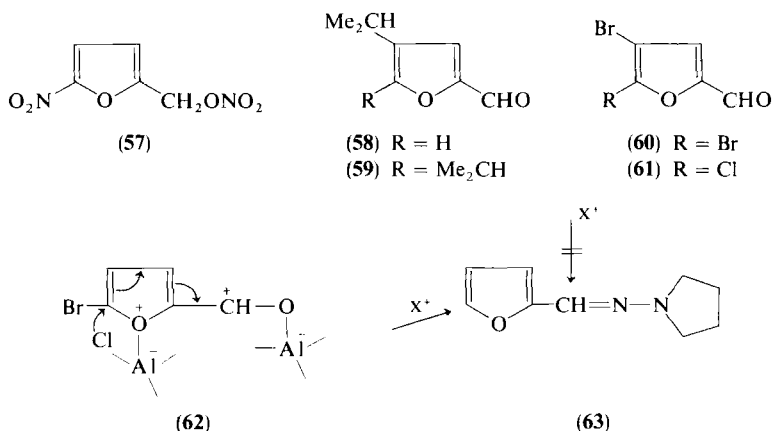
¹⁴⁰ S. M. Abdel-Wahhab and L. S. El-Assal, *J. Chem. Soc. C*, 867 (1968).

¹⁴¹ G. Doddi, F. Stegel, and M. T. Tanesi, *J. Org. Chem.* **43**, 4303 (1978).

¹⁴² G. Ciranni and S. Clementi, *Tetrahedron Lett.*, 3833 (1971).

detail. Acylation of furan with acetic anhydride under various conditions produced α/β ratios between 800 and 6,800 and required isotopic analysis (^{14}C) for the necessary precision. Partial rate factors reveal that the "unreactive" 3(4) position is highly reactive, much more so than a benzene position.

The dominance of 2(5)-substitution sometimes is not observed. The chief products (**58**, **59**) obtained by alkylating furan-2-carboxaldehyde with 2-chloropropane and aluminum chloride are due to 4-substitution. The authors provide an explanation based on Hückel LCAO calculations which indicate that "superdelocalizability" in the aldehyde is higher at the 4 than at the 3 position and so is the charge q .¹⁴³ They also point out that a Friedel-Crafts catalyst can alter orientations typical of benzene compounds by coordinating with a heteroatom, producing in effect a much more electronegative substituent. When forced to completion by the use of a large excess of "catalyst," the method is called "the swamping catalyst effect;" meta positions are little altered while the coordination deactivates the "ortho" and "para" positions. In a 2-acylfuran this means the α/β ratio will alter in favor of 4-substitution. The use of this technique is summarized by Soviet workers.¹⁴⁴ Recent studies



show that bromination of furan-2-carboxaldehyde in an excess of aluminium chloride gives not only the useful 4,5-dibromo aldehyde **60** but also the 4-bromo-5-chloro compound **61**.¹⁴⁵ An exchange occurs within a Lewis salt, perhaps as in **62**.¹⁴⁵ Coordination to carbonyl oxygen is well known, and coordination could occur between the Lewis acid and the heterocyclic oxygen

¹⁴³ M. Valenta and I. Koubek, *Collect. Czech. Chem. Commun.* **41**, 78 (1976).

¹⁴⁴ Ja. L. Goldfarb, Ju. B. Volkenstein, and L. I. Belenkii, *Angew. Chem., Int. Ed. Engl.* **7**, 519 (1968).

¹⁴⁵ B.-P. Roques, M.-C. Zaluski, M. Bonhomme, and M. Robba, *Bull. Soc. Chim. Fr.*, 242 (1971); B.-P. Roques, M.-C. Fournie-Zaluski, and R. Oberlin, *ibid.*, 2334 (1975).

atom as well. *Ab initio* LCAO-SCF calculations suggest that in furan the charge tends to stay on the oxygen atom whereas in pyrrole it is more dispersed among the carbon atoms.¹⁴⁶

Politzer *et al.*¹⁴⁷ have computed the potential for the furan molecule using a deorthogonalized CNDO/2 molecular wave function and found this potential to be positive everywhere except near the oxygen atom where it is negative. Still more striking is the fact that, when a hydrogen atom at any position was moved out of plane into a tetrahedral position, a negative potential developed along the fourth tetrahedral bonds. This is the direction of approach by an electrophile. Since the 2 and 5 position are close to the oxygen atom the three adjacent negative areas tend to coalesce giving a large negative volume capable of attracting an electrophile and it is this effect that might account for selective substitution at the 2(5)-position, for the negative volumes near the 3(4)-positions are small and isolated. The calculated CNDO/2 atomic charges for the 2(5)-carbons are positive, those for the 3(4)-carbons negative, in either planar or part tetrahedral forms. Taken alone, this fact predicts quite the wrong orientation.

An examination of the products formed by bromination of furan disclosed only addition. These were very unstable and could not be isolated but NMR analyses showed that both 2,5-dibromo-2,5-dihydrofuran (*cis* and *trans*) and 2,3-dibromo-2,3-dihydrofuran (*trans* only) were formed. Eventually only 2-bromofuran is left, but whether the additions are side equilibria or genuine stages on the way to the substitution product is not yet known.¹⁴⁸

Individual substitutions may not necessarily be true electrophilic aromatic substitution reactions. Usually it is assumed that they are, however, and with this assumption the furan nucleus can be compared with others. For trifluoroacetylation by trifluoroacetic anhydride at 75°C relative rates have been established, by means of competition experiments,¹⁴⁹ thiophene, 1; selenophene, 6.5; furan, 1.4×10^2 ; 2-methylfuran, 1.2×10^5 ; pyrrole, 5.3×10^7 . While nitrogen is usually a better source of electrons for an incoming electrophile (as in pyrrole versus furan) there are exceptions. For example, the "enamine" **63** reacts with Eschenmoser's salt at the 5-position and not at the enamine grouping.¹⁵⁰ Also amusing is an attempted Fischer indole synthesis in which a furan ring is near the reaction site and diverted the reaction into a pyrazole synthesis.¹⁵¹

¹⁴⁶ D. Chou and H. Weinstein, *Tetrahedron* **34**, 275 (1978).

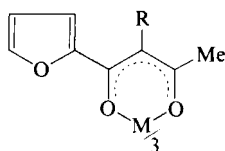
¹⁴⁷ P. Politzer, R. A. Donnelly, and K. C. Daiker, *J. C. S. Chem. Commun.*, 617 (1973); P. Politzer and H. Weinstein, *Tetrahedron* **31**, 915 (1975).

¹⁴⁸ E. Baciocchi, S. Clementi, and G. V. Sebastiani, *J. C. S. Chem. Commun.*, 875 (1975).

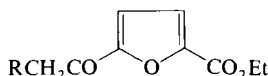
¹⁴⁹ S. Clementi and G. Marino, *Tetrahedron* **25**, 4599 (1969).

¹⁵⁰ R. Brehme and H. E. Nikolajewski, *Tetrahedron* **32**, 731 (1976).

¹⁵¹ B. S. Holla and S. Y. Ambekar, *J. C. S. Chem. Commun.*, 221 (1979).



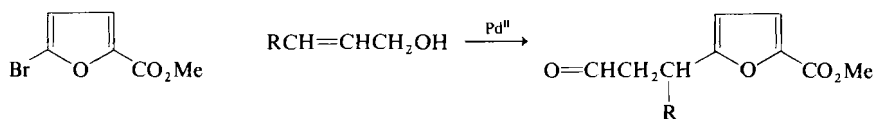
- (64) R = H
 (65) R = NO₂
 (66) R = Br



- (67) R = H
 (68) R = CH₃CO

Two exceptions to substitution at the furan ring are interesting. Nitration by Cu(NO₃)₂ of the chromium (or cobalt) chelates **64** occurs at the chelate ring giving nitro compounds **65**, and bromination by *N*-bromosuccinimide gives the bromo compounds **66**.¹⁵² Even the gentle acylation required to convert ethyl 2-furoate into the 5-acetyl derivative **67** (acetic anhydride with SnCl₄) has to be controlled carefully because a second acylation is possible—not on the ring, but on the side chain. The product is the diketone **68**.¹⁵³

Attack by palladium π -complexes has the character of electrophilic substitution, the order of decreasing reactivity for typical aromatic compounds being furan, ferrocene, naphthalene, benzene.¹⁵⁴ According to a review,¹⁵⁵ the reaction between furan and styrene in the presence of Pd(OAc)₂ affords both 2-styrylfuran and 2,5-distyrylfuran in poor yield. Other reports state that if the substituent R in the alkene RCH=CH₂ is bulky the product will be entirely in the *E* configuration, otherwise it will be a mixture of geometric isomers.¹⁵⁶ In contrast, the reaction between furan and palladium malonate is said to furnish 2-furoic acid in quantitative yield.¹⁵⁷ The following complex conversion is catalyzed by palladium(II) acetate in hexamethylphosphoramide buffered by triphenylphosphine and sodium hydrogen carbonate and is the subject of a Japanese patent¹⁵⁸:



¹⁵² T. Sasaki, K. Kanemata, and G. Kinoshita, *J. Org. Chem.* **33**, 680 (1968); *J. Chem. Soc. C*, 951 (1969).

¹⁵³ R. Ercoli, E. Mantica, G. Claudia, S. Dhiozzotto, and E. Santambrogio, *J. Org. Chem.* **32**, 2917 (1967).

¹⁵⁴ Y. Fujiwara, R. Asano, I. Moritani, and S. Teranishi, *J. Org. Chem.* **41**, 1681 (1976); C. A. Mansfield, *Proc. Int. Conf. Coord. Chem.*, 16th (1974) [*C. A.* **85**, 176633 (1976)].

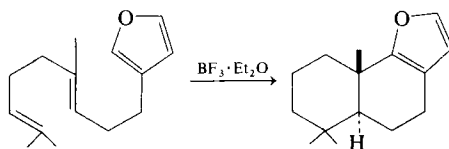
¹⁵⁵ I. Moritani and Y. Fujiwara, *Synthesis*, 524 (1973).

¹⁵⁶ G. Maruyama, M. Yoshidomi, Y. Fujiwara, and H. Taniguchi, *Chem. Lett.*, 1229 (1979).

¹⁵⁷ T. Sakadibara and Y. Odira, *J. Org. Chem.* **41**, 2049 (1976).

¹⁵⁸ Z. Yoshida, T. Tamara, and Y. Yameda, *Jpn. Kokai Tokkyo Koho* 79 32463.

Furans possessing alkene side chains can be cyclized by acids¹⁵⁹⁻¹⁶²; sulfonic acids have been used¹⁵⁹ although boron fluoride etherate is now preferred. Such reactions have been applied in the solidagenone series¹⁵⁹ and are particularly important for the so-called furanosesquiterpenoids from marine sponges, the pallescensins.¹⁶⁰⁻¹⁶² Illustrated in Scheme 28 is a cyclization of a geranylmethylfuran; the terminal epoxide reacts similarly yielding the corresponding alcohol with high stereoselectivity.¹⁶⁰⁻¹⁶²

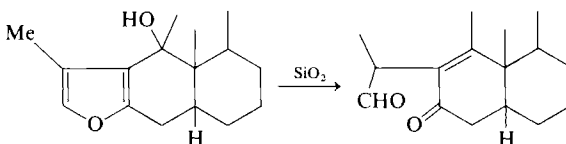


SCHEME 28

Acid-catalyzed condensation of ketones with furans gives 2,2'-methylene-bisfurans and eventually, if both 2(5)-positions are free, the quaterenes mentioned in Section XI.A.¹⁶³

B. PROTONATION

Protonation is the simplest form of electrophilic attack; in furan it leads to polymerization since the ring can open to polyfunctional products or the protonated species can act as an electrophile and attack another furan molecule, so most work has to be on substituted furans. Even so, the naturally occurring trialkyl furan, petasalbin, is cleaved by so mild a "reagent" as silica¹⁶⁴:



¹⁵⁹ T. Anthonsen, P. H. McCrindle, R. D. H. Murray, and G. A. R. Young, *Tetrahedron* **26**, 3091 (1970).

¹⁶⁰ G. Cimino, S. De Stefano, A. Guerriero, and L. Minale, *Tetrahedron Lett.*, 1425, 3723 (1975).

¹⁶¹ T. Matsumoto and S. Usui, *Chem. Lett.*, 105 (1978).

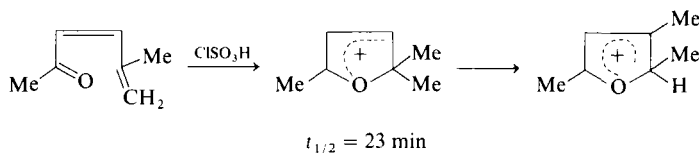
¹⁶² D. Nasipuri and G. Das, *J. C. S. Perkin I*, 2776 (1979).

¹⁶³ S. Pennanen and G. Nyman, *Acta Chem. Scand.* **26**, 1018 (1972); A. Ishigaki and T. Shono, *Bull. Chem. Soc. Jpn.* **47**, 1467 (1974); J. A. Hirsch and A. J. Szur, *Tetrahedron* **28**, 2961 (1972); W. H. Brown, B. J. Hutchinson, and M. H. MacKinnon, *Can. J. Chem.* **49**, 4017 (1971).

¹⁶⁴ L. Norotny and K. Kotva, *Collect. Czech. Chem. Commun.* **39**, 2949 (1974).

According to the above general discussion of electrophilic attack a proton should add at position 2(5); evidence has been obtained for 2-methylfuran which, in the presence of acid and D_2O undergoes isotopic replacement at the 5-position as shown by NMR analysis. After that a slow diminution takes place in all the other proton signals. Therefore, in contrast to earlier suggestions, protonation at the 2(5)-position cannot be the rate determining step in acid-catalyzed ring opening reactions.¹⁶⁵ The rate of proton exchange is subject to isotope effects and exhibits the activation parameters of an $A-S_E2$ mechanism for aromatic substitution with a Wheland-type transition state.¹⁶⁶ Polymerization occurs almost exclusively if an α -position is free and polymers appear to be formed before there is any evidence for ring opening. But no β -exchange is found, so β -protonation could be the rate-controlling step in the ring-opening reaction.¹⁶⁶ This again contrasts with earlier views.¹⁶⁷ Accordingly, acid-catalyzed isotope exchange is commonly employed to prepare α -deuterated furans, whereas the β -deuterated analogues have to be prepared by indirect methods.¹²⁸ Isotopic exchange can be promoted by salts¹⁶⁸ such as $NiCl_2$ and also by bases (see below).

Alkyl migration has not been found in protonated furan derivatives. Neither 2,5-dimethylfuran nor 2,3,5-trimethylfuran undergo any change other than protonation in fluorosulfonic acid containing antimony pentafluoride. On the other hand, migrations will occur during cyclization until the product corresponds to a protonated furan (Scheme 29).¹⁹



SCHEME 29

Katritzky and his colleagues have used equilibrium protonation to estimate the aromaticity of furan and similar heterocycles using 2,5-di-*tert*-butylfuran as substrate in sulfuric acid. In agreement with the foregoing discussion, the furan does not behave as a Hammett (i.e., oxygen) base but as a carbon base similar to azulene. On Reagan's H_e scale, the furan gave $n = 1.22$, correspond-

¹⁶⁵ A. Kankaanpera and S. Kleemola, *Acta Chem. Scand.* **23**, 3607 (1969).

¹⁶⁶ P. Salomaa, A. Kankaanpera, E. Nikander, K. Kaipainen, and R. Aaltonen, *Acta Chem. Scand.* **27**, 153 (1973).

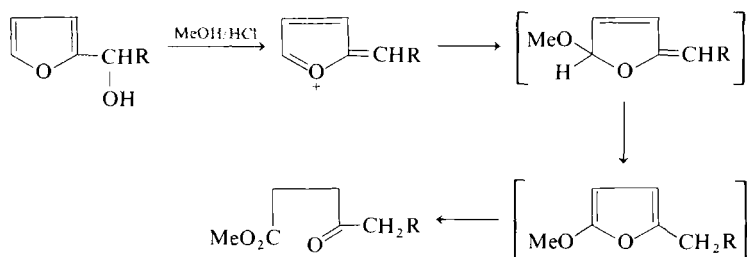
¹⁶⁷ K. Unverferth and K. Schwetlick, *J. Prakt. Chem.* **312**, 882 (1970).

¹⁶⁸ G. E. Calf and J. L. Garnett, *Aust. J. Chem.* **21**, 1221 (1968).

ing to $pK_a - 10.01$, a much lower (and more realistic) figure than had been obtained previously. After making allowance for the *tert*-butyl groups the pK_a for furan itself was estimated to be -13 ± 1 and led to a value of 18 ± 5 kcal/mol for the aromaticity, well within the thermochemically derived range 15.8 to 23 kcal/mol.¹⁶⁹

Italian workers have calculated geometries and energies should the proton become attached to oxygen as in most ethers. *Ab initio* SCF data show that all the atoms remained in plane except the proton on the oxygen atom, which in the most stable geometry was slightly out of plane. The barrier to inversion is only 1.3 kcal/mol and the tendency of the oxygen atom to prefer the pyramidal conformation is small. The proton retains much of the positive charge and the negative charge on oxygen is not much reduced, nor is the π -interaction strongly affected. Differences in thiophene protonation are much larger.¹⁷⁰ Hydrogen bonding with furan oxygen as acceptor is sometimes assumed to be significant; whether the view is valid seems uncertain.^{170a}

Furylcarbinols with protic acids (fluoroboric acid) may merely give carbenium (furylium) salts.¹⁷¹ Similar cations are accessible via 2-furyldiazomethane derivatives,¹⁷² but in many cases ring opening and prototropic shifts ensue as in Marckwald reactions (Scheme 30).¹⁷³ A recent development controls solution acidity by using magnesium or zinc ions instead of protons



SCHEME 30

¹⁶⁹ M. P. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron* **32**, 1767 (1976).

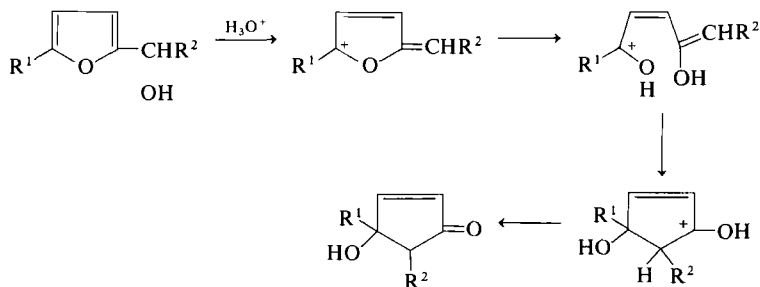
¹⁷⁰ F. Bernadi, *Gazz. Chim. Ital.* **107**, 55 (1977).

^{170a} A. Jurasek, M. Breza, and R. Kada, *Collect. Czech. Chem. Commun.* **37**, 2246 (1972); V. Knoppova, A. Jurasek, and V. Voros, *ibid.* **42**, 3175 (1977).

¹⁷¹ A. J. Castro, G. Tertzakian, B. T. Nakata, and D. A. Bose, *Tetrahedron* **23**, 4499 (1967); V. Ramanathan and R. Levine, *J. Org. Chem.* **27**, 1216 (1962); A. Fabrycy and Z. Wichert, *Tetrahedron Lett.* 1307 (1977); J. J. Basselier and J. P. Le Roux, *Bull. Soc. Chim. Fr.*, 4443 (1971).

¹⁷² R. V. Hoffman and H. Shechter, *J. Org. Chem.* **39**, 2938 (1974).

¹⁷³ H. Stetter and H. Kuhlmann, *Tetrahedron* **33**, 353 (1977).



SCHEME 31

thus avoiding the Marckwald reaction and allowing the intermediates to cyclize to cyclopentanone derivatives connected with prostaglandin studies.¹⁷⁴ The route is generalized in Scheme 31. Pennanen describes some remarkable acid-catalyzed transformations of carbinols including a redox dismutation in furoin.¹⁷⁵ As might be expected, furancarboxamides are protonated on the amide oxygen atom, and the 2-isomers are less basic than the 3-isomers.¹⁷⁶

C. NUCLEOPHILES

Protons are easily detached from the furan nucleus, especially when some activating group is present. Even the carbonate ion will catalyze the deuteration of position 5 in 2-furoic acid salt.¹⁷⁷ And 40% NaOD in D₂O, will catalyze the replacement of all the nuclear protons giving the fully deuterated product. The acid can be converted into *d*₄-furan by treatment with mercury salts, and then DCl.¹⁷⁸ For general synthetic purposes it is now usual to obtain nuclear carbanions by lithiation as described in Section IV.

After 20 years pharmacological interest in nitrofurans is as strong as ever, and still prompts studies including nucleophilic substitutions. Kinetic studies of the replacement of halogen by dimethylamine in 5-halo-2-nitrofurans yield second order rate constants and disclose spectroscopic (IR, UV, and

¹⁷⁴ G. Piancatelli, A. Scettri, G. David, and M. D'Auria, *Tetrahedron* **34**, 2775 (1978); G. Piancatelli and B. Scettri, *ibid.* **33**, 69 (1977); G. Piancatelli, A. Scettri, and S. Barbadoro, *Tetrahedron Lett.*, 3555 (1976).

¹⁷⁵ S. Pennanen, *Acta Chem. Scand.* **27**, 3133 (1973).

¹⁷⁶ G. Alberghina, S. Fisichella, and G. Musumara, *J. S. Perkin II*, 1700 (1979).

¹⁷⁷ D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J. C. S. Perkin I*, 201 (1973).

¹⁷⁸ J. A. Zoltewicz and H. L. Jacobsen, *J. Heterocycl. Chem.* **8**, 331 (1971).

PMR) trends that correspond to relative rates.¹⁷⁹ From an examination of the displacement of chloride from 1-chloro-5-nitrofuran by potassium iodide in acetic acid or by sodium sulfide in water it was concluded that the substitution need not be a true nucleophilic substitution. Initially there could be a transfer of one electron from the nucleophile to the furan nucleus; the resultant radical anion loses chloride to form a furyl radical and product.¹⁷⁹

The formyl group provides enough activation so that lithium fluoride will convert 5-bromofuran-2-carboxaldehyde into 5-fluorofuran-2-carboxaldehyde, but only in dimethylformamide at 100°C. Other metal cations are ineffective. Replacement by other halogens is easy, the chloride-bromide displacement being reversible.¹⁸⁰

The halogen in 5-bromofuran-2-carboxaldehyde is readily displaced by aromatic thiols, and the aromatic residue can be provided by pyridazine, benzeneselenazole, benzimidazole, benzoxazole, etc. as well as benzene.¹⁸¹

Amines tend to give more complex results. The compound obtained by treating a 5-halofuran-2-carboxaldehyde with aniline is now thought to have a structure resulting from anil formation, halogen displacement, protropy and protonation. The free base is too unstable to be studied easily but acetylation of the salt provides readily recognizable products.¹⁸² A related example is discussed later (Section X,A,2).

Lieb and Eiter¹⁸³ have studied the interesting problem posed by 5-nitrofuran-2-carboxaldehyde in which both substituents are activating and capable of reacting in different ways. Most nucleophiles (azide, sulfide, sulfinate, xanthate) displace the nitro group. Enamines react mainly in the usual way with the aldehyde group giving aldol condensation products, but there is also a more complex reaction in which the nitro group is lost (Scheme 32). Other workers¹³³ find that hydrogen bromide converts the nitro compound into 5-bromofuran-2-carboxaldehyde with loss of the nitro group, possibly because the formyl group will be protonated and so have its electrophilicity greatly increased (Scheme 32).¹⁸⁴

Czech workers have examined displacements in substituted malononitriles in which the double bond transmits the double effect of the cyanide groups

¹⁷⁹ V. N. Novikov and S. V. Borodev, *Khim. Geterotsikl. Soedin.*, 1316 (1976); V. N. Novikov, Z. N. Nazarova, L. D. Babeshkina, and T. F. Mikhailova *Kratk. Tezisy-Vses. Soveshch. Probl. Mekh. Geteroliticheskikh Reacts.*, 53 (1974). [*CA* **85**, 77138 (1976)].

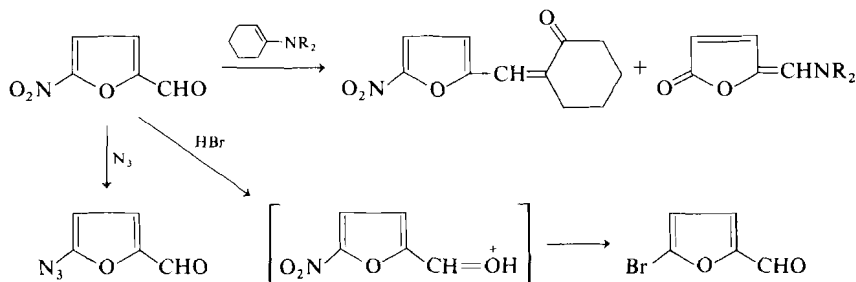
¹⁸⁰ R. Mocelo and V. Pustovarov, *Sobre Deriv. Cana Azucar* **9**, 29 (1975); R. Mocelo and E. Fanghanel *Ciencias, Ser. 3* **12**, (1972).

¹⁸¹ R. Kada and J. Kovac, *Chem. Zvesti* **29**, 402 (1975).

¹⁸² E. Niwa, *Chem. Ber.* **103**, 2992 (1970).

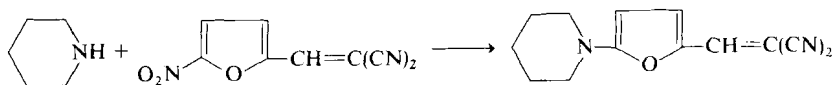
¹⁸³ F. Lieb and K. Eiter, *Justus Liebigs Ann. Chem.* **761**, 130 (1972).

¹⁸⁴ H. R. Snyder and P. H. Seehausen, *J. Heterocycl. Chem.* **10**, 385 (1973).



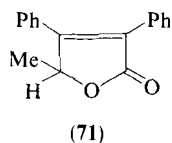
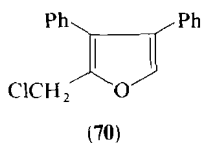
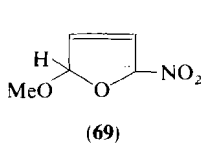
SCHEME 32

into the ring.¹⁸⁵ Scheme 33 shows a nitro group being displaced by a secondary amine. In such circumstances they find that the nitro group is the most readily displaced, the order being $\text{NO}_2 > \text{Br} > \text{PhSO}_2 > \text{PhS}$.¹⁸⁶



SCHEME 33

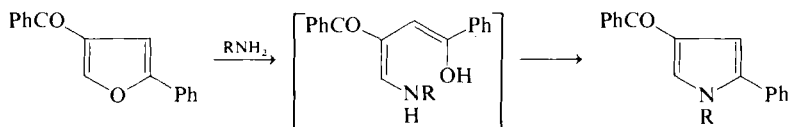
Such nucleophilic displacements are likely to be addition-elimination reactions, whether or not radical anions are also interposed as intermediates. The addition of methoxide ion to 2-nitrofuran in methanol or dimethyl sulfoxide affords a deep red salt of the anion **69**; PMR shows the 5-proton has the greatest upfield shift, the 3- and 4-protons remaining vinylic in type.¹⁸⁷ The similar additions in the thiophene series are less complete, presumably because oxygen is relatively electronegative and the furan aromaticity relatively low. Additional electronegative substituents increase the rate of addition and a second nitro group makes it necessary to use stopped flow techniques of rate measurement.¹⁴¹ In contrast, one acyl group (benzoyl or carboxy) does not stabilize an addition product and seldom promotes nucleophilic substitution by weaker nucleophiles such as ammonia. Whereas



¹⁸⁵ I. Srokova, A. Jurasek, M. Dandarova, and K. Kovac, *Collect. Czech. Chem. Commun.* **43**, 3253 (1978); R. Kada, *Synth. Commun.* **7**, 157 (1977).

¹⁸⁶ V. Knoppova, R. Kada, and J. Kovac, *Collect. Czech. Chem. Commun.* **44**, 2417 (1979).

¹⁸⁷ G. Doddi, A. Poretti, and F. Stegel, *J. Heterocycl. Chem.* **11**, 97 (1974).

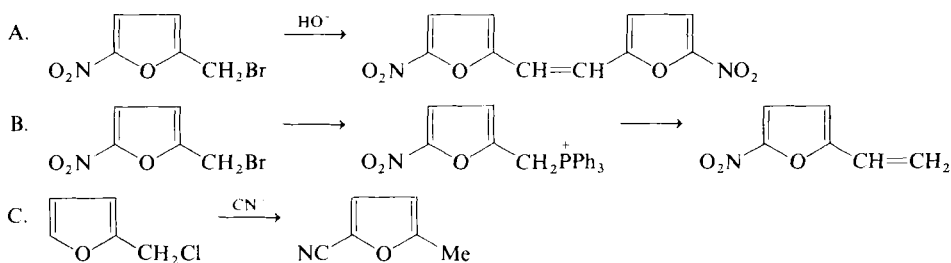


SCHEME 34

4-benzoyl-2-phenylfuran does not react well with ammonia, it reacts smoothly with primary amines to give pyrroles (Scheme 34).¹⁸⁸

When forced, reactions with ammonia commonly lead to derivatives of pyrrole or pyridine, e.g., 2-furoic acid at 210°C gives 2-amino-3-hydroxyri-dine.¹⁸⁹ Hydrazine is a better nucleophile and attacks 3-acylfurans in hot ethanol; if there is no group to be displaced the ring opens and a pyrazole is formed.¹⁹⁰

2-Bromomethyl-5-nitrofuran offers an incoming nucleophile a choice of reaction sites; product formation seems to be determined mainly by the nature of the nucleophile but is also strongly dependent upon the solvent and other conditions. The hard base hydroxide ion removes a methylenic proton from the "active methylene" group and the new nucleophile displaces bromide from another molecule to produce, eventually, the bis(5-nitro-2-furyl)ethene (Scheme 35, A).¹⁹¹



SCHEME 35

In contrast, triphenylphosphine displaces bromide smoothly and the Wittig reaction then possible provides the recommended synthesis of 2-nitro-5-vinylfuran as sketched in scheme 35, B.¹⁹² Halomethylfurans and cyanide ion give nuclear substitution, as has long been known (Scheme 35, C). Nuclear substitutions occur for 2,5-bis(chloromethyl)furan,¹⁹³ but are less

¹⁸⁸ D. E. Weiss and N. H. Cromwell, *J. Heterocycl. Chem.* **11**, 905 (1974).

¹⁸⁹ H. Greuter and D. Bellus, *J. Heterocycl. Chem.* **14**, 203 (1977).

¹⁹⁰ G. Menichi and M. Hubert-Habart, *Bull. Soc. Chim. Fr.*, 1235 (1977).

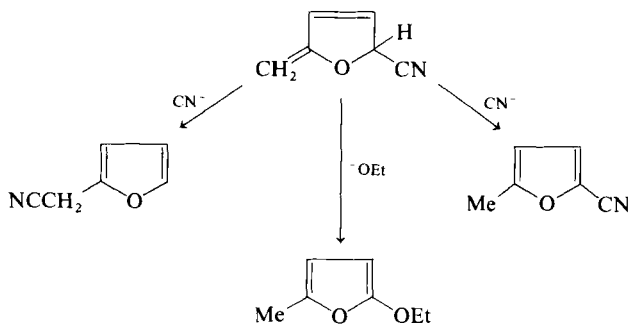
¹⁹¹ J. Prousek, A. Jurasek, and J. Kovac, *Collect. Czech. Chem. Commun.* **44**, 2511 (1979).

¹⁹² D. Vegh, J. Kovac, and M. Dandarova, *Collect. Czech. Chem. Commun.* **44**, 1630 (1979).

¹⁹³ K. Yu. Novitskii, Kh. Gresl, and Yu. K. Yur'er, *Khim. Geterotsikl. Soedin.*, 289 (1966).

important with methyl 5-chloromethyl-2-furoate^{194,195} and methyl 2-chloromethyl-3-furoate^{43,195} although in these esters the methylene group is active enough to allow dimer formation as in Scheme 35, A. Similarly, 3-chloromethylfuran affords a mixture of nitriles. Pure 3-furanacetonitrile has to be procured by decarboxylating the corresponding 2-furoic acid.¹⁹⁶ Pure 2-furanacetonitrile can in fact be made quite easily from 2-chloromethylfuran by conducting the nucleophilic displacement in dimethyl sulfoxide; other solvents, even dimethylformamide, give mixtures.¹⁹³

That the intermediate formed in Scheme 35 C must be the exomethylene compound shown in Scheme 36 had been recognized long before it was isolated and found to be unexpectedly stable except to bases.¹⁹⁷ Cyanide ion induces isomerization to the furonitrile by prototropic shift. Other bases cannot be used in place of cyanide ion because they displace the cyano group already present in a substitution of an unusual kind (Scheme 36).¹⁹⁷



SCHEME 36

Cyanide is not the only nucleophile to effect reactions as in Scheme 35, C, but of those studied so far only benzenesulfinate and phenoxide are similar (and also show second order kinetics) while others give simple substitution with no rearrangement (and show first order kinetics). No doubt ionization to a furylium ion plays an important part in some of these transformations, but it is harder to account for the behavior of **70** which yields a lactone (**71**) and almost no cyano products.¹⁹⁸

A technique has been recommended for converting furylcarbinols via halides into nitriles that dispenses with the need to isolate the intermediate

¹⁹⁴ T. M. Cresp and M. V. Sargent, *Aust. J. Chem.* **27**, 905 (1974).

¹⁹⁵ C. Rivalle, E. Bisagni, and J.-M. Lhoste, *J. Heterocycl. Chem.* **13**, 89 (1976).

¹⁹⁶ M. Caviou, *Bull. Soc. Chim. Fr.*, II, 271 (1978).

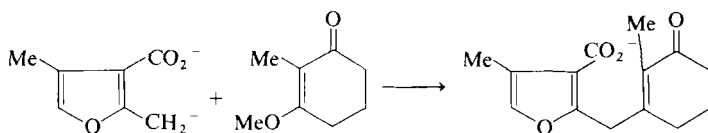
¹⁹⁷ S. Divald, M. C. Chun, and M. M. Joullié, *Tetrahedron Lett.*, 777 (1970); *J. Org. Chem.* **41**, 2835 (1976).

¹⁹⁸ K. Yamamoto and A. Tanaka, *J. Heterocycl. Chem.* **16**, 1293 (1979).

halide, but 5-aryl groups were invariably present so its generality is undefined.¹⁹⁹

Carbanionic centers can be generated next to the furan ring if moderate activation is available, but the temperature has to be kept low $\sim -70^{\circ}\text{C}$) otherwise internal nucleophilic attack opens the ring.²⁰⁰ At low temperature, therefore, 2-furylcarbanions are useful for attaching side chains while at room temperature they offer an excellent entry into allene chemistry that virtually reverses some of the furan syntheses discussed earlier.²⁰⁰ The corresponding 3-furylcarbanions are usually more stable and react with prenyl donors in syntheses of the naturally occurring furans perillene and dendrolasin.²⁰¹ Other pertinent examples are discussed in Section IV.

Lithium diisopropylamide removes a proton from a methyl group adjacent to carboxyl, and a 2(5)-methyl group is preferred to a 3(4)-methyl group, perhaps because of the electronegativity of the ring oxygen atom. The



technique forms the basis of a simple synthesis of (\pm)-ligularone, the key step being nucleophilic substitution.²⁰² If there is not enough stabilization for the anionic center then collapse of the furan ring occurs even at low temperatures. Atsumi and Kuwajima²⁰³ trap the cumulene alcohols produced from chloromethylfurans as their trimethylsilyl ethers and find that cumulene hydrogen can also be replaced by silyl groups thus greatly increasing the scope for further elaboration; they give references to allied work. In their latest work they employ furyllithium with silylating agents in a remarkably smooth variation outlined in Scheme 37.²⁰⁴

Grignard reagents (methyl, ethyl, *tert*-butyl, benzyl) are not powerful enough to attack the furan ring unless it is conjugated with a carbonyl group in which case conjugate additions are usual and afford substituted furans and/or dihydrofurans.²⁰⁵ Even amines readily attack furans bearing carbonyl substituents, especially if there are two; in this case the system

¹⁹⁹ J. A. Foulkes and J. Hutton, *Synth. Commun.* **9**, 625 (1979).

²⁰⁰ M. J. Taschner and G. A. Kraus, *J. Org. Chem.* **43**, 4235 (1978).

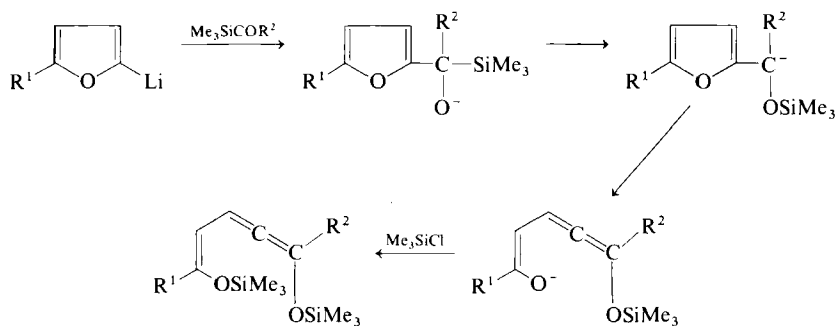
²⁰¹ A. Hoppmann and P. Weyerstahl, *Tetrahedron* **34**, 1723 (1978).

²⁰² M. Tada, Y. Sugimoto, and T. Takahashi, *Chem. Lett.*, 1441 (1979).

²⁰³ K. Atsumi and I. Kuwajima, *J. Am. Chem. Soc.* **101**, 2208 (1979).

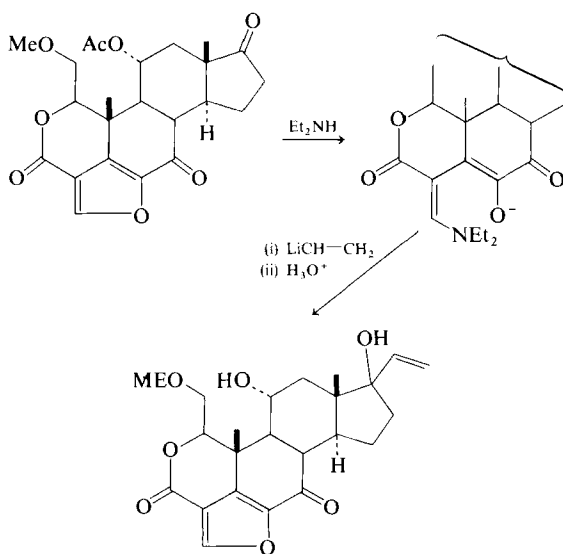
²⁰⁴ I. Kuwajima, K. Atsumi, T. Tanaka, and T. Inone, *Chem. Lett.*, 1239 (1979).

²⁰⁵ R. Sjöholm, *Acta Chem. Scand., Ser. B* **B32**, 105 (1978); **B31**, 278 (1977); G.-A. Holmberg, L. Jalander, H. Norrgård, and B. Pettersson, *ibid.* **B28**, 909 (1974).



SCHEME 37

behaves as a vinylogous ester. Haefliger and Hauser describe an excellent example²⁰⁶; they used the reaction to protect the furan ring in wortmannin while attacking another part of the molecule with vinylolithium as sketched in Scheme 38. The more common situation with primary amines was discussed in connection with Scheme 34.



SCHEME 38

²⁰⁶ W. Haefliger and D. Hauser, *Helv. Chim. Acta* **58**, 1629 (1975).

IV. Lithium, Boron, and Other Elements

A. METALS

1. *Lithium and Potassium*

The years under review have been dominated by lithium compounds almost to the exclusion of other metals, especially alkali metals. However, butylpotassium and butylcesium deprotonate furans at position 2 or 5 at -60°C , and the carbanions accept carbon dioxide giving furan-2-carboxylic acids in poor yield and react with 1,4-dibromobutane to give derivatives of 2,2'-butylenebisfuran.²⁰⁷ The common reagent is one of the isomeric butyllithiums although others are possible; phenyllithium can also specifically deprotonate furans at the 2(5)-position.²⁰⁸ Earlier workers using temperatures near room temperature found furyllithium reactions difficult to control. For example, reactions with acids give 2-acylfurans mixed with varying amounts of difurylcarbinols.²⁰⁹ It is now a matter of course to use the lowest practicable temperature and to exclude oxygen. Contact of oxygen with 2-furyllithium produces the furylbutenolide **72** and the difuryldiketone **73**; in a long sequence of reactions, oxygen forms a lactone which then reacts with more of the organometallic derivative as sketched briefly in Scheme 39.²⁰⁸

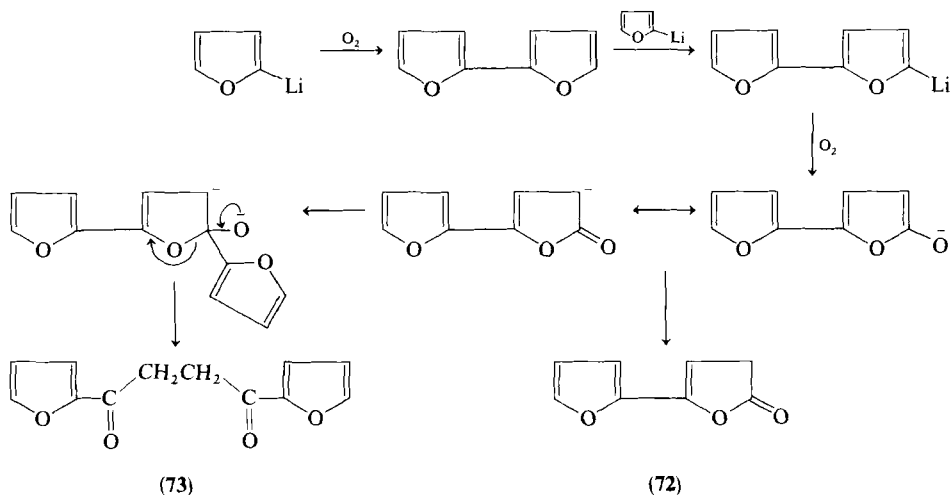
Of several groups,¹²⁵⁻¹²⁸ the French have been particularly adept at developing the use of lithiations in connection with polyhalogen compounds.¹²⁵ Just as butyllithium effects selective α -deprotonation it will also remove α -bromine in preference to β -bromine although (unlike hydrogen) this can be removed subsequently. Here we have the basis for the synthesis of furan-2,3,5-tricarbaldehyde as shown in Scheme 40.¹²⁵ Furan-2,3,5-tricarbaldehyde has been obtained for the first time by the use of this method, though not completely pure. Labeled dimethylformamide affords deuterioformyl furans.¹²⁵ Attention should also be paid to the intermediate bromocarbanions, which show no tendency to collapse into 2,3-didehydrofuran, an analogue of benzyne. In another interesting study 3,4-diiodofuran was converted to the dilithium compound **74** and carboxylated to furan-3,4-dicarboxylic acid.²¹⁰ In the same work the existence of monolithium derivative **75** was demonstrated and no sign of 3,4-didehydrofuran was noted. Further,

²⁰⁷ P. Benoit and N. Collignon, *Bull. Soc. Chim. Fr.*, 1302 (1975).

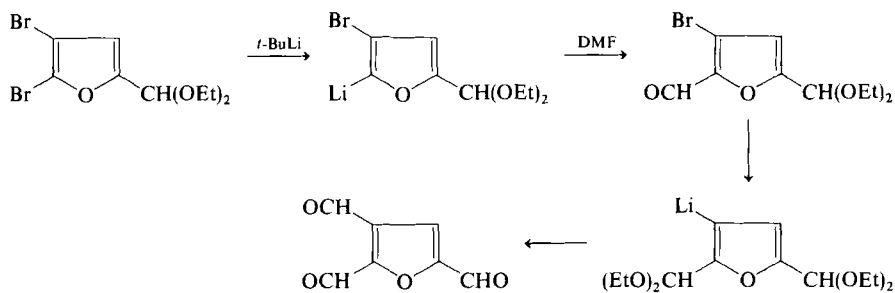
²⁰⁸ E. Niwa and M. Miyake, *Chem. Ber* **102**, 1443 (1969); **103**, 997 (1970).

²⁰⁹ C. H. Heathcock, L. G. Gulick, and T. Dehlinger, *J. Heterocycl. Chem.* **6**, 141 (1969).

²¹⁰ M.-C. Azulski, M. Robba, and M. Bonhomme, *Bull. Soc. Chim. Fr.*, 1838 (1970).

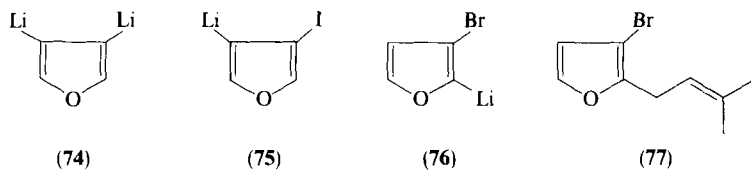


SCHEME 39



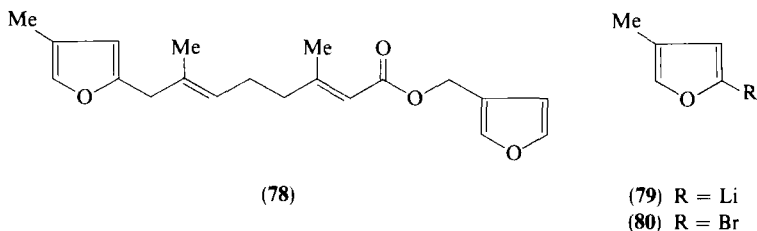
SCHEME 40

a β -halogen atom may direct deprotonation to an adjacent α -site. In contrast to butyllithium, which simply converts 3-bromofuran into 3-furyllithium, lithium diisopropylamide (LDA) removes the 2-proton adjacent to the halogen giving **76**. Elegant syntheses of 2,3-dialkylfurans are possible in consequence. With prenyl bromide, **76** affords **77** whence it is but a step to rosefuran (**48**).²¹¹

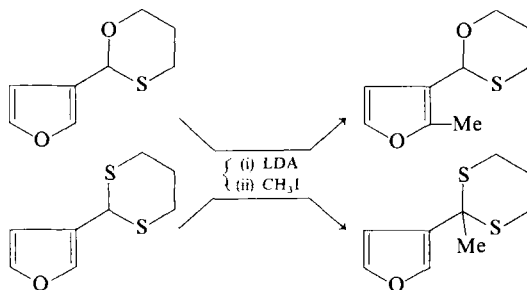


²¹¹ N. D. Ly and M. Schlosser, *Helv. Chim. Acta* **60**, 2085 (1977).

Very many naturally occurring 3-alkyl- or 3-acylfurans are now routinely synthesized by preparing a substrate for treatment with 3-furyllithium, itself made from 3-bromofuran according to Fukuyama, Tokoroyama, and Kubota, who used it to obtain pyroangensolide and fraxinellone.²¹² Equally, 2-lithiofuran is used for such natural products as the acetylenic furans from *Alphonsea ventricosa*²¹³ and other compounds.²¹⁴ For the synthesis of the sesquiterpenoid sponge-metabolite pleraplysillin-2 **78**, the lithiofuran **79** and therefore the bromofuran **80** was needed to secure the orientation; a suitable preparation was devised for **80**.²¹⁵



There is considerable regioselection within the lithiation process itself, especially with the gentler reagent lithium diisopropylamide. As noted a halogen directed lithium into the adjacent 2-position. This is also true for several oxygen- or sulfur-containing substituents at a 3-position, the lithium entering position 2; a subtle example is seen in Scheme 41 where regioselectivity (ring versus side-chain lithiation) is controlled by the number of adjacent sulfur atoms.²¹⁶ Another means of control is discussed in the section on tin



SCHEME 41

²¹² Y. Fukuyama, T. Tokoroyama, and T. Kubota, *Tetrahedron Lett.*, 3401 (1972); 4869 (1973).

²¹³ F. Bohlmann, F. Stohr, and J. Stafeldt, *Chem. Ber.* **111**, 3146 (1978).

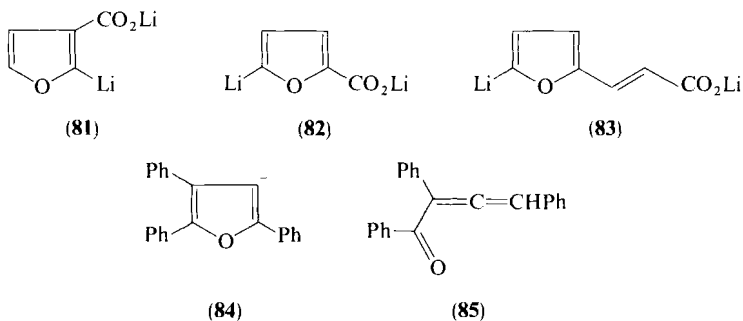
²¹⁴ J. Wrobel, J. Cybulski, and Z. Dabrowski, *Synthesis*, 686 (1977); A. J. Arco, M. H. Trammell, and J. D. White, *J. Org. Chem.* **41**, 2075 (1976).

²¹⁵ D. W. Knight, *Tetrahedron Lett.*, 469 (1979).

²¹⁶ H. J. Reich, P. M. Gold, and F. Chow, *Tetrahedron Lett.*, 4433 (1979).

compounds. At -20°C instead of -78°C , however, even two sulfur atoms do not provide enough stabilization and the ring collapses to an allenic system.²¹⁷

Recent discoveries by Knight²¹⁵ strongly indicate there may be considerable orientational control within the lithiation process itself. The direction of lithiation by halogen noted above involved the use of lithium diisopropylamide which on general grounds must be considered a much gentler reagent than butyllithium and correspondingly more selective. Knight observed that this reagent removes from 3-furoic acid only the 2-proton (not the 5-) giving **81** and was able to obtain 3-furoic acids with deuterium, alkyl groups, or carbinol groups at the 2-position with great ease. Perhaps this is expected, since ordinary bases remove the 2(5) proton in 2-furoic acids, while lithio species are well known to be stabilized by oxygen and nitrogen "ortho" substituents, yet a parallel study of 2-furoic acid disclosed an equal facility in the formation of the 5-lithio derivative **82** and an equal participation in characteristic carbanion reactions. Even 2-furylacrylic is converted into its 5-lithio derivative **83**, though not so efficiently.²¹⁵



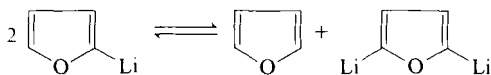
Few furan 3-carbanions are stable except at low temperatures and only recently have they been extensively used. Ring opening is common. Gilchrist and Pearson²¹⁸ report that the fate of the unusually stable carbanion **84** depends upon both solvent and temperature. At room temperature and in benzene it partly opens giving the allenic ketone **85**; in ether it is fairly stable. In hexane, the 3-lithiofuran is precipitated unless heated to 65°C when it isomerizes to acetylenic salts giving the allenic ketone **85** with water.

The solvent can be important for 2-lithiofurans as well. Chadwick and Willbe²¹⁹ report that in the tetra-*N*-methylethylenediamine the enhanced ionicity of the organometallic species allows an equilibrium to be set up

²¹⁷ M. J. Taschner and G. A. Kraus, *J. Org. Chem.* **43**, 4235 (1978).

²¹⁸ T. L. Gilchrist and D. P. J. Pearson, *J. C. S. Perkin I*, 989 (1976).

²¹⁹ D. J. Chadwick and C. Willbe, *J. C. S. Perkin I*, 887 (1977).

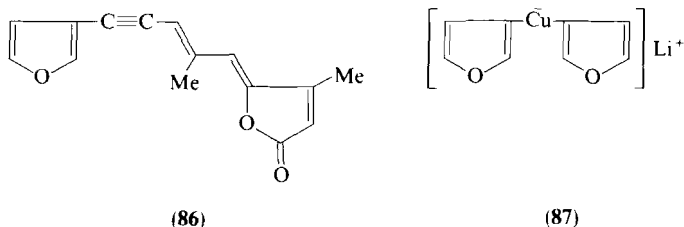


SCHEME 42

(Scheme 42) such that carboxylation, for example, leads to a mixture of 2-furoic acid and 2,5-furandicarboxylic acid. High yields of the dilithiated furan are readily obtained by adjusting the conditions.

2. Copper

Copper derivatives of furan were first used for Ullmann coupling reactions. They are made from the appropriate lithiofuran and copper(I) iodide or copper(I) bromide and at 115°C with aryl halides in pyridine or at -45°C with acetylenic iodides in tetrahydrofuran,²²⁰⁻²²² as for example in a synthesis of the highly unsaturated furan freelingyne **86** from *Eremophila freelingii*.²²² Free hydroxy and amino groups can be protected as trimethylsilyl or tetrahydropyranyl derivatives to provide a simple route to hydroxy- or aminoarylfurans.²²⁰ The yields are not high, but are much lower if the metal and halogen are interchanged in the reactants because then the chief products are difurans and diaryls or diacetylenes.²²²



We owe to Kato and his colleagues a considerable advance in furan copper reagents. They have demonstrated the formation of the lithium di(3-furyl) cuprate species **87** which is highly reactive and possesses "hard" properties that suit it to reaction at "hard" centers, mainly carbonyl carbon.²²³ The reagent is easily prepared *in situ* from 3-furyllithium and Cu_2I_2 . Simple copper derivatives do not react with ketones, but this cuprate reacts well and quantitatively with acid chlorides. It also reacts well with some epoxides (oxirans). Moreover, there is another form prepared in the presence of

²²⁰ F. D. King and D. R. M. Walton, *Synthesis*, 40 (1976).

²²¹ C. Ullenius, *Acta Chem. Scand.* **26**, 3383 (1972).

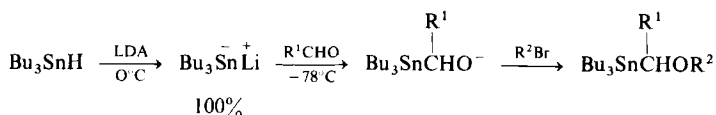
²²² D. W. Knight and G. Pattenden, *J. C. S. Perkin I*, 635, 641 (1975).

²²³ Y. Kojima, S. Wakita, and N. Kota, *Tetrahedron Lett.*, 4577 (1979); Y. Kojima, N. Kato, and Y. Terada, *ibid.*, 4667.

of dimethyl sulfide, which appears to contain the sulfide in a complex. This complex has "soft" characteristics and is highly suitable for reaction with alkyl halides to form alkylfurans or for Michael additions to unsaturated ketones. In this form the reagent is somewhat sensitive to light and needs protection, but it reacts with homogeranyl bromide to give dendrolasin (**88**) in 78% yield. There is yet another reagent in this series, discovered because of the use of butyllithium in excess. It has the general constitution $\text{LiCu}(\text{C}_4\text{H}_3\text{O})_2 \cdot 2\text{C}_4\text{H}_3\text{OLi}$ and is believed to have a tetrahedral cluster structure. It is a more powerful nucleophile than the simpler cuprate, but has not yet been explored in depth.

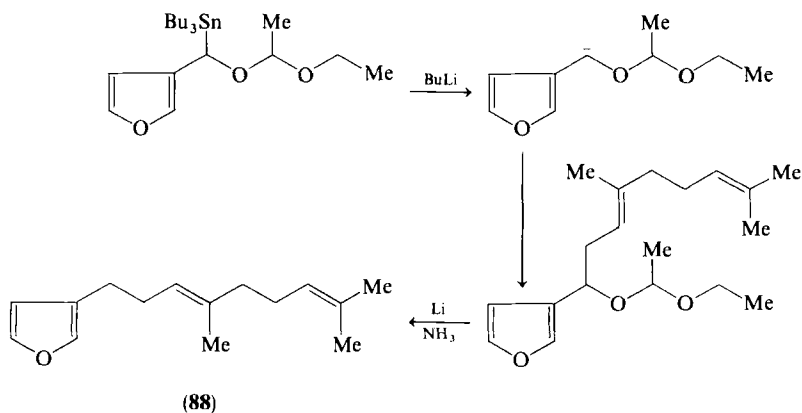
3. Tin

Tin has received a little attention. With lithium diisopropylamide, tributylstannane gives the stannate readily and this adds easily to carbonyl groups. The alkoxide product is stabilized as an ether (Scheme 43):



SCHEME 43

The tin can now be displaced by butyllithium to give a carbanion and a new group attached Scheme 44 shows the nub of a synthesis of dendrolasin (**88**) which illustrates the use of the tin reagent to avoid the 2-alkylation that would otherwise occur²²⁴ (cf. Scheme 41).



SCHEME 44

²²⁴ W. C. Still, *J. Am. Chem. Soc.* **100**, 1481 (1978).

2-Bromofurans give Grignard reagents when attacked by copper–magnesium in tetrahydrofuran but, while the products can be alkylated, etc., in the expected way, no clear advantage has emerged.²²⁵

4. Mercury

Mercury compounds are still much in use though the vogue has lessened. Bis(2-furyl)mercury has been found to be a weak electron acceptor able to attach ligands such as 1,10-phenanthroline²²⁶ while the UV photoelectron spectrum implicates 6p orbitals in bonding and indicates a weak electron-releasing capability about that of the methyl group.²²⁷ The known selective orientation of the mercuration reaction is still valued¹²⁷ and the mercury compounds themselves can be alkylated giving syntheses of sesquirose-furan²²⁸ and longifolin²²⁹ or they can be treated with lithium metal to displace the mercury and so lead into the lithiofuran sequences.²³⁰ Together with *N*-bromsuccinimide, mercury(II) chloride converts furan in one step into 5,5'-dibromo-2,2'-difuran,²³¹ perhaps via an organomercury intermediate, and such intermediates probably play an important part in some of the furan syntheses based upon the cyclization of acetylenes and they can sometimes be isolated.⁷⁰ The mercury derivative of a furanoid sheep liver toxin from *Tetradymia glabrata* was used for X-ray structural analysis.²³²

B. NONMETALS

1. Boron

Furan-2-boronic acid (**89**) and furan-3-boronic acid are readily prepared by interaction of the furyllithium with methyl borate (MeO)₃B followed by acid hydrolysis.^{233,234} Like most boronic acids they owe their acidity more to coordination with a water molecule than to simple proton transfer; they

²²⁵ A. Takeda, K. Shinham, and S. Tsuboi, *Bull. Chem. Soc. Jpn.* **50**, 1903 (1977).

²²⁶ N. A. Bell and R. M. King, *J. Organomet. Chem.* **179**, 133 (1979).

²²⁷ F. P. Colonna, G. Distefano, M. Guerra, D. Jones, and A. Modelli, *J. C. S. Dalton*, 2037 (1979).

²²⁸ Y. Gopichand, R. S. Prasad, and K. K. Chakravarti, *Tetrahedron Lett.*, 5177 (1973).

²²⁹ N. Fukamiya and S. Yasuda, *Chem. Ind. (London)*, 126 (1979).

²³⁰ G. Büchi, E. Sz. Kovats, P. Enggist, and G. Uhde, *J. Org. Chem.* **33**, 1227 (1968).

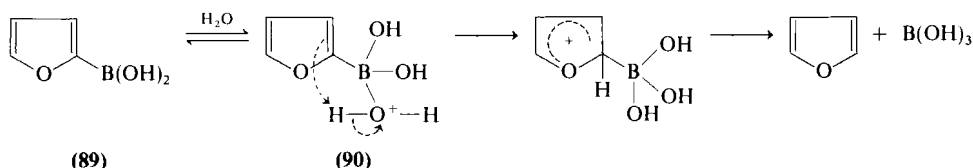
²³¹ J. Reisch and I. Mester, *Chem. Ber.* **112**, 1493 (1979).

²³² P. W. Jennings, S. K. Reeder, J. C. Hurley, C. N. Caughlan, and G. D. Smith, *J. Org. Chem.* **39**, 3392 (1974).

²³³ B. P. Roques, D. Florentin, and M. Callanquin, *J. Heterocycl. Chem.* **12**, 195 (1975).

²³⁴ D. Florentin, B. P. Roques, and M. C. Fournie-Zaluski, *Bull. Soc. Chim. Fr.*, 1999 (1976).

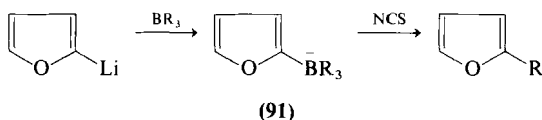
show expected behavior, i.e., the 2-isomer is more acidic (pK 7.89) than the 3-isomer (pK 8.65) and this is more acidic than benzeneboronic acid. Evidently the ring oxygen atom exerts its accustomed electronegative effect.²³³ Protodeboronation follows the same pattern but the mechanism is not a straightforward electrophilic substitution because rate studies establish (i) a strongly negative activation entropy, (ii) a rate reduction by electron attracting substituents and a rate increase by donors, and (iii) an isotope effect greater than unity.²³⁵ Again coordination with a water molecule might be an essential preliminary as indicated in diagram 90 in Scheme 45.



SCHEME 45

Several formylfuranboronic acids and similar compounds have been prepared by regular methods and studied with respect to their ^{13}C and ^1H NMR spectra. As in the benzene series, the protons "ortho" to the boron are deshielded and the "meta" protons are shielded. Good conjugation exists between the furan ring (donor) and both the boron atom and the carbonyl group (acceptors). A Hammett-Jaffé analysis yielded $\sigma_p^+ + 0.256$ for the $\text{B}(\text{OH})_2$ group.²³⁴

2-Furyllithium reacts rapidly with trialkylborons though the furylborons **91** believed to be formed are not actually isolated. Treated with an electrophile (iodine or *N*-chlorosuccinimide), they transfer one alkyl residue to the furan ring and eject the boron residue in a reaction well known in other series (Scheme 46). The 2-alkylfurans are indeed produced in excellent yields and the method is better than many other syntheses.²³⁶

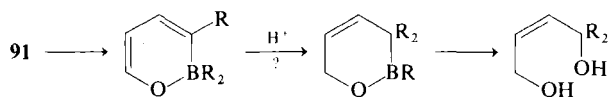


SCHEME 46

Earlier it had been found that interaction without additional electrophile led to transfer of two alkyl groups and ring opening to enediols with specific

²³⁵ D. Florentin, M. C. Fournie-Zaluski, M. Callanquin, and B. P. Rogers, *J. Heterocycl. Chem.* **13**, 1265 (1976).

²³⁶ E. R. Marinelli and A. B. Levy, *Tetrahedron Lett.*, 2313 (1979).



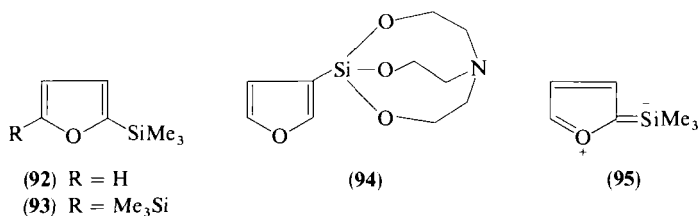
SCHEME 47

cis configuration,²³⁷ though later authors suggest that the result may have depended upon the addition of acid as part of the workup procedure.²³⁶ The net result is a reversal of one of the standard syntheses of the furan ring (Scheme 47).

Furanborinic acids have hardly been studied except for a report of their use in the synthesis of biaryls, e.g., 2-(2-thienyl)furan in 20% yield.²³⁸

2. Silicon

That furan can be attacked by more active electrophiles including chlorotrimethylsilane has long been known.²³⁹ Once again, however, lithiation provides a much more controllable alternative. 2-Furyllithium reacts with chlorotrimethylsilane to give **92** and the lithiation sequence can be repeated giving the silane **93**.²⁴⁰ Compounds containing silicon are often active physiologically, the silatrane **94** and the 2-furyl isomer exhibiting neurotropic activity in mice.²⁴¹ Other furylsiloxanes have been obtained from 2-(dichloro)methylsilylfuran.²⁴²



Pinkerton and Thames have carried out a new, more extensive study of *pd*- π -bonding in silicon substituted furans and have slightly modified the earlier, Soviet conclusions. The aromatic protons indicate by their chemical shifts at infinite dilution that there are simultaneous but opposing +I and

²³⁷ A. Suzuki, N. Miyaara, and M. Itoh, *Tetrahedron* **27**, 2775 (1971).

²³⁸ G. M. Davies, P. S. Davies, W. E. Paget, and J. M. Wardleworth, *Tetrahedron Lett.*, 795 (1976).

²³⁹ D. E. Pearson and C. A. Buckle, *Synthesis*, 533 (1972).

²⁴⁰ S. F. Thomas, L. H. Edwards, T. N. Jacobs, P. L. Grube, and F. H. Pinkerton, *J. Heterocycl. Chem.* **9**, 1259 (1972).

²⁴¹ E. Lukevics, S. Germane, O. A. Pudova, and N. Ereka, *Khim.-Farm. Zh.* **13**, 52 (1979).

²⁴² W. C. Hammann, C. F. Hobbs, and D. J. Bauer, *J. Org. Chem.* **32**, 2841 (1967).

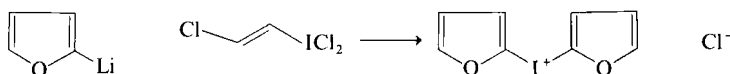
—M effects consistent with the interaction depicted in **95**. The extent of the *pd*- π -bonding seems to vary with the substituents, electron withdrawal being greatest in aldehydes, less in esters, and least in acetals.²⁴³ (See also Section XII,B,5.)

3. Phosphorus

Furanphosphonic acid derivatives (including sulfur analogues) are available by interaction of the nearly ubiquitous furyllithium reagents with halides ClP(X)(OR)_2 , where X is oxygen or sulfur.²⁴⁴ Furylphosphonium salts show a tendency to disobey the usual rule that alkali removes the group giving the most stable carbanion; if both furyl and benzyl residues are present, either may be lost (as furan or toluene) leaving a phosphine oxide.²⁴⁵ It is unlikely that the result has any direct relation to the electronegativity of the oxygen atom. An electrochemical preparation of furylphosphonium salts is mentioned in Section VI,A,1.

4. Iodine

Furyliodonium salts can be made by the following reaction, though perhaps less easily than had been claimed earlier.^{246,247}



Such iodine is easily replaced by several nucleophiles. Methoxide displaces it to give methoxyfuran, and thiocyanate to give furyl thiocyanate, but phenoxide ion fails.²⁴⁸

V. Radical Chemistry

A. SIMPLE RADICALS

The manner in which radicals attack furans has been studied deeply and earlier misconceptions have been corrected, especially the idea that anodic oxidation in methanol involves methoxy radicals.²⁴⁸ Furan cation radi-

²⁴³ F. H. Pinkerton and S. F. Thames, *J. Heterocycl. Chem.* **7**, 747 (1970).

²⁴⁴ S. Andreae and H. Seeboth, *Z. Chem.* **19**, 98 (1979).

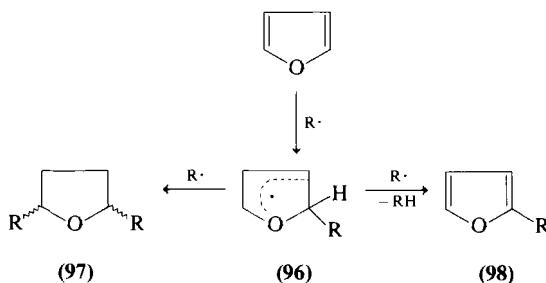
²⁴⁵ D. W. Allen and B. G. Hutley, *J. C. S. Perkin I*, 675 (1978).

²⁴⁶ F. M. Beringer and R.-A. Nathan, *J. Org. Chem.* **35**, 2095 (1970).

²⁴⁷ S. Gronowitz and B. Holm, *J. Heterocycl. Chem.* **14**, 281 (1977).

²⁴⁸ K. E. Kolb and C. L. Wilson, *J. C. S. Chem. Commun.* 271 (1966).

cals are often the recognised intermediates, as explained in Section VI,B,1, but many reactions are not well understood and are vaguely classified as radicals. It remains the case, however, that radicals attack the furan nucleus first at the 2-position giving an intermediate radical (96) which can then (i) add another radical at the 5-position thus leading to a 2,5-disubstituted dihydrofuran (97), or (ii) lose a hydrogen atom thus leading to a substituted furan (98). These modes are shown in Scheme 48; there are other possibilities, such as radical dimerization, but the two shown are the chief ones.



SCHEME 48

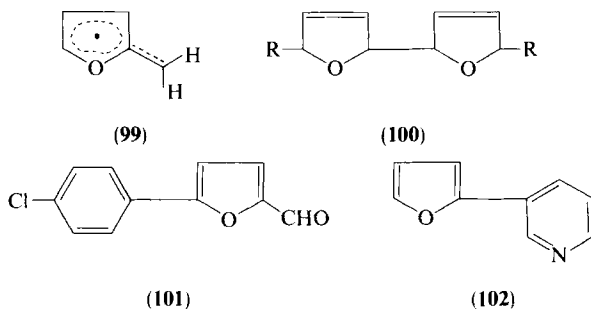
Generated from diacetyl peroxide, methyl radicals attack 2-methylfuran at position 5 preferentially; if both 2- and 5-positions are occupied as in 2,5-dimethylfuran there is still little or no attack at the 3(4)-position. If there is a choice of 2(5)-positions, as in 3-methylfuran, then that adjacent to the methyl substituent is selected.²⁴⁹ These orientation rules are very like those for electrophilic substitution, but are predicted for radical attack by calculations of superdelocalizability (S_r) by the simple HMO method. Radical bromination by *N*-bromsuccinimide follows theory less closely, presumably because it does not occur through a pure radical-chain mechanism.²⁴⁹

In the foregoing work the methyl groups already present were never attacked by the radicals whereas they are quite sensitive to *tert*-butoxy radicals generated photochemically from *tert*-butyl peroxide between -30 and -80°C . 2-Methylfuran yields the furfuryl radical **99** which exhibits an ESR spectrum of 32 lines confirming that the two methylenic hydrogen atoms are nonequivalent. INDO calculations agree well with the observed hyperfine splitting constants provided that the bond length from C-2 to the methylene carbon is optimized. The calculations show that the planar

²⁴⁹ M. Janda, J. Srogl, I. Stibor, M. Nemec, and P. Vopatrna, *Tetrahedron Lett.*, 637 (1973); J. Srogl, M. Janda, V. Skála, P. Trska, M. Ryska, and I. Stibor, *Collect. Czech. Chem. Commun.* **39**, 3109 (1974).

rotamer is more stable than the perpendicular rotamer by about 25 kcal/mol.²⁵⁰ The same radical has been obtained by γ -radiolysis of 2-methylfuran supported by an adamantane matrix at room temperature but some uncertainty was experienced in assigning the vinylic proton coupling constants and in the similar radical from 2,5-dimethylfuran the resolution was too poor to distinguish between the methylene protons.²⁵¹

Monitored by ESR spectroscopy, the continuous radiolysis of furan derivatives in water leads, in effect, to the addition of the hydroxy group at the 2-position; ring opening of the resultant radical is rapid.^{251a}



Furan appears to capture benzoyloxy radicals before they lose carbon dioxide; with benzoyl peroxide at 35–80°C, furan yields the stereoisomeric 2,5-dibenzoates of structure **97** ($R = \text{PhCO}_2$) with almost no carbon dioxide evolution.²⁵² 2,5-Dimethylfuran is also very reactive but undergoes attack at the methyl groups, 5-methylfurfuryl benzoate resulting; 2-methylfuran exhibits intermediate behavior and undergoes both types of attack.²⁵³ Aromatic thiyl radicals react differently, showing a strong preference for 2,3-disubstitution, an orientation that is usually unimportant with other radicals. The reason is thought not properly to lie with the radical but with the way in which it is made, which is by treating 4-bromobenzenethiol with hydrogen peroxide and an iron(III) catalyst. The key intermediate is therefore a cation, not a radical; the suggested mechanism is depicted in Scheme 49. The role allocated to the iron cation is confirmed by the fact that, in the absence of the iron catalyst, the reaction is confined to the usual 2-substitution.²⁵⁴

²⁵⁰ L. D. Kispert, R. C. Quijano, and C. U. Pittman, *J. Org. Chem.* **36**, 3837 (1971).

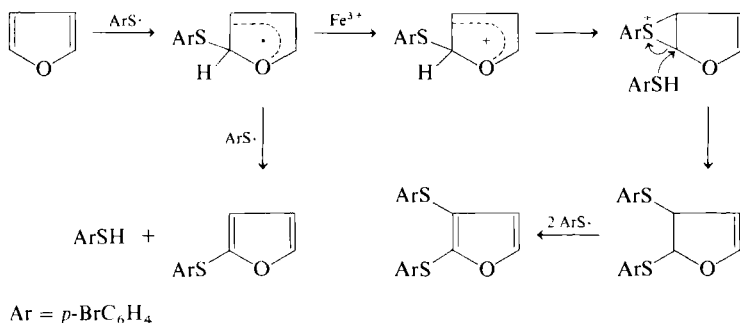
²⁵¹ D. L. Winters and A. C. Ling, *Can. J. Chem.* **54**, 1971 (1976).

^{251a} R. H. Schuler, G. P. Laroff, and R. W. Fessenden, *J. Phys. Chem.* **77**, 456 (1973).

²⁵² K. E. Kolb and W. A. Black, *J. C. S. Chem. Commun.*, 1119 (1969).

²⁵³ J. I. G. Cadogan, J. R. Mitchell, and J. T. Sharp, *J. C. S. Chem. Commun.* 1433 (1971).

²⁵⁴ L. Benati, C. M. Camaggi, and G. Zanardi, *J. Org. Chem.* **40**, 966 (1975).



SCHEME 49

Since furans react readily with radicals they can interfere with radical chains and so with radical polymerization of vinylic monomers. Monomers containing a furan nucleus exhibit autoinhibition as a result, so the matter is of industrial importance. Gandini and Rieumont²⁵⁵ have looked at this problem, using the routine initiator azobisisobutyronitrile as a source of radicals at 70°C. Most of the furans studied gave three kinds of product; furan itself gave a 2,5-addition product (32%) of type **97**, a 2,3-addition product (10%), and dimers represented by **100** (17%). The only marked contrast came from 2-vinylfuran which supplied oligomers with no trace of materials containing dihydrofuran units, so it seems that, if the vinyl group is in conjugation, it protects the furan ring by reacting preferentially. Vinyl 2-furoate gave oligomers containing "dihydrofuranic units," though other interpretations of some of these facts had been made earlier by a different group.²⁵⁶ Similarly studies with *tert*-butyl peroxide as initiator proved to be futile because this merely converted the furans into brown resins containing neither furan nor dihydrofuran rings.²⁵⁵ Again, 2-methyl-5-vinylfuran underwent only vinylic polymerization, and it was concluded that inhibition occurs when the furan ring accepts a radical at the 2(5)-position giving a new radical of type **96** (Scheme 48) too stable to continue the normal propagation. The methyl group is thought to hinder the approach of the growing radical to the 2(5)-position thus allowing normal polymerization to proceed.²⁵⁵

Only in a few arylations of furans are radicals clearly responsible, though many others are conventionally regarded as radical or radicaloid in character. Since there is often no definite evidence, we consider all arylations together for convenience.

²⁵⁵ A. Gandini and J. Rieumont, *Tetrahedron Lett.*, 2101 (1976).

²⁵⁶ I. Morita, Y. Kato, B. Kamo, and S. Furusawa, *Chuo Daigaku Rikogakubu Kiyo* **16**, 139 (1973).

For the arylation of furans by the Gomberg reaction the slow generation of aryl radicals from diazonium salts stabilized by zinc chloride is prescribed for success.²⁵⁷ The Gomberg–Hey method (generation from nitrosoacetanilides) and the pyrolysis of benzoyl peroxides are also still in use.²⁵⁸ Increasing in popularity is generation from diazoaminobenzenes and isopentyl nitrite at about 30°C in an aprotic medium.²⁵⁹ But whatever method is used, arylation initially attacks on the 2(5)-positions and yields are in the range 30–40%.^{258–262} A 2-substituent already present affects the rate of arylation to a small extent but seems not to alter the orientation; thus furfural (furan-2-carbaldehyde) reacts more readily with the 4-chlorophenyl radical than does 2-methylfuran, but it is still the 5-position that is attacked giving **101**.²⁶⁰ The tendency to attack the 2(5)-positions is indeed very great, for both positions react if enough reagent is available, and it is reported that an acetyl group can be extruded (as acetaldehyde) by an incoming aryl group.²⁶¹

It is now a recognized phenomenon that radicals attack substituted aromatic compounds including furan at the ipso position, sometimes displacing the substituent originally present. Unsymmetrical 2,5-disubstituted furans accept a radical at either α -position leading to two series of reactions shown as A and B in Scheme 50 where the 1-adamantyl radical is shown reacting with methyl 5-nitro-2-furoate. A characteristic of nitrofuran is also seen; by some means the nitro group appears to rearrange to a nitrite substituent which can then collapse into NO and a substituted butenolide much as in photolysis (Section VII). Furthermore, NO₂ released by the initial substitution process can itself add to the nitrofuran giving a *gem*-dinitro compound which is thermally unstable, collapsing at about 140°C into nitrogen oxides and the same butenolide (Scheme 50).²⁶³

Meerwein–Gomberg reactions between pyridinediazonium salts and furans fail because the Sandmeyer reaction supervenes, and the isopentyl nitrite method also gives poor results.²⁶⁴ Fortunately, photolysis of 3-

²⁵⁷ D. C. Ayres and J. R. Smith, *J. Chem. Soc. C*, 2737 (1968).

²⁵⁸ L. Benati, C. M. Camaggi, M. Tiecco, and A. Tundo, *J. Heterocycl. Chem.* **9**, 919 (1972).

²⁵⁹ L. Fisera, J. Kovac, E. Komonova, and J. Lesko, *Tetrahedron* **30**, 4123 (1974); L. Fisera, J. Lesko, J. Kovac, B. Hasova, and P. Azulpsky, *Collect. Czech Chem. Commun.* **41**, 3398 (1976); A. Krutosikova, J. Kovac, and V. Sykora, *ibid.* **39**, 1892 (1974).

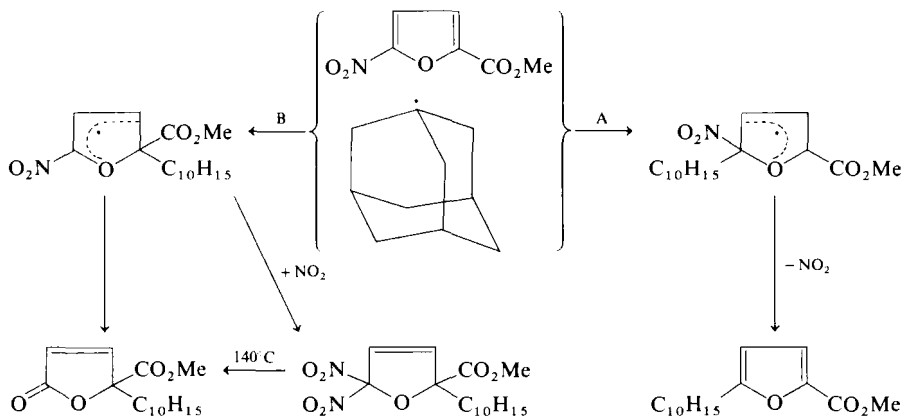
²⁶⁰ M. A. Khan and J. B. Polya, *Aust. J. Chem.* **26**, 1147 (1973).

²⁶¹ I. G. Markova, M. K. Polievktov, A. F. Oleinik, and G. A. Modhikova, *Khim. Geterotsikl. Soedin.*, 598 (1976); D. R. Shrikhar, C. V. R. Sastry, M. Jogibhukta, S. R. Moorthy, N. K. Vaidya, and P. G. Reddy, *Org. Prep. Proced. Int.* **8**, 302 (1976); S. Farinas, C. R. Rodriguez Palacio, and I. Ramas Raimundo, *CENTRO, Ser.: Quim. Tecnol. Quim.* **5**, 75 (1977).

²⁶² G. Vermin, J. Kister, and J. Metzger, *Helv. Chim. Acta* **62**, 21 (1979).

²⁶³ P. Cogolli, L. Testaferri, M. Tiecco, and M. Tingoli, *J. C. S. Chem. Commun.*, 890 (1976).

²⁶⁴ L. Fisera, J. Lesko, J. Kovac, J. Hrabovsky, and J. Sura, *Collect. Czech. Chem. Commun.* **42**, 105 (1977).



SCHEME 50

iodopyridine is furan gives rather good yields (64%) of 3-(2-furyl)pyridine (**102**); attack by a 3-pyridyl radical is suggested but not proved.²⁶⁵ Reactions of the Ullman type are also reported. Furylacetylenes are obtained from 2-iodofuran and copper(I) acetylides in pyridine.²⁶⁶ and 2-furylcopper(I) reacts fairly well with aryl halides to give 2-arylfurans in the same solvent (see also Section IV,A,2) provided that any amino or hydroxy groups are protected by trimethylsilylation.²²⁰ 2,2'-Difuryl (2,2'-difuran) and its analogues are also available via Ullmann reactions,²⁶⁷ while furan itself is transformed into 5,5'-dibromo-2,2'-difuran by a combination of mercury(II) chloride and *N*-bromosuccinimide.²³¹

Since aryl radicals can be electrophilic it is not surprising to find that the partial rate factors for arylation of furan by 4-X-C₆H₄ radicals show a linear correlation with σ^+ , the rate increasing with electronegative substituents X.²⁵⁸ If the electron withdrawing character of the reagent is increased too much, however, a major change in reaction occurs because the precursor diazonium salt is rendered rather stable to thermal collapse thus giving time for the diazonium group itself to enter into reactions.¹³⁵ For example 2,4-dinitrobenzenediazonium sulfate in aqueous acetic acid converts 2,5-dimethylfuran into the azo compound **103** in what looks like an ordinary coupling reaction. The reaction is strongly affected by the conditions, especially the solvent. With the diazonium fluoroborate instead of the sulfate and with dioxane as solvent the reaction with 2,5-dimethylfuran

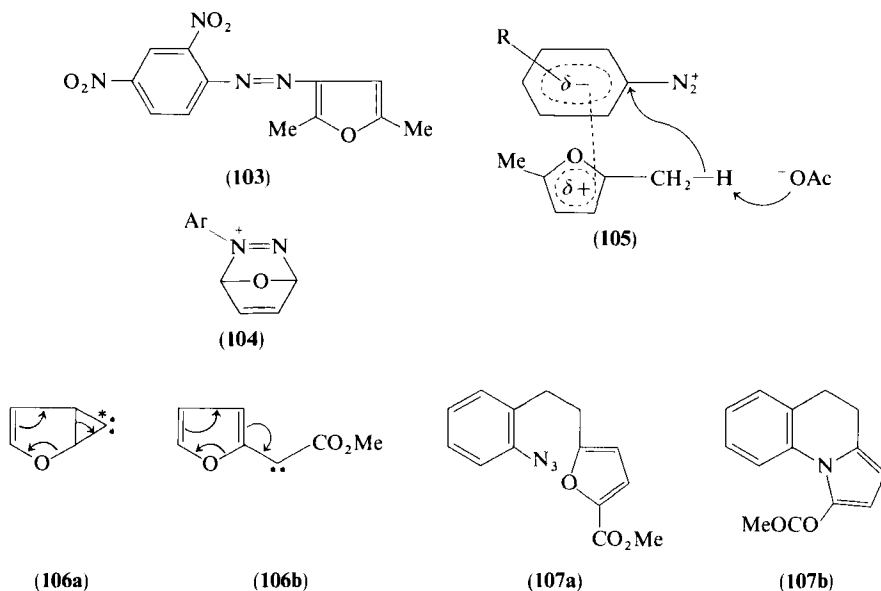
²⁶⁵ H.-S. Ryang and H. Sakurai, *J. C. S. Chem. Commun.*, 595 (1972).

²⁶⁶ R. E. Atkinson, R. E. Curtiss, and J. A. Taylor, *J. Chem. Soc. C*, 558 (1967).

²⁶⁷ P. E. Fanta, *Synthesis*, 9 (1974); M. Goshaev, O. S. Otroshchenko, and A. A. Sadykov, *Russ. Chem. Rev. (Engl. Transl.)* **41**, 12 (1972).

leads to attachment not at the nucleus but to a methyl group. And if the solvent is changed to acetic anhydride containing sodium acetate, the product is a hydrated form of **103**. Certain variations are reasonably explained as examples where the diazonium group is active enough to undertake cycloadditions leading to the unstable system in **104** and hence to the products, but for several reactions it appears necessary to assume a tautomeric state for the furan that is not likely to be accessible under most conditions where the acidity is low. The cycloaddition of active diazonium salts is established, and the idea is further supported by the inability of benzofurans to undergo any reaction but Gomberg arylation.¹³⁵

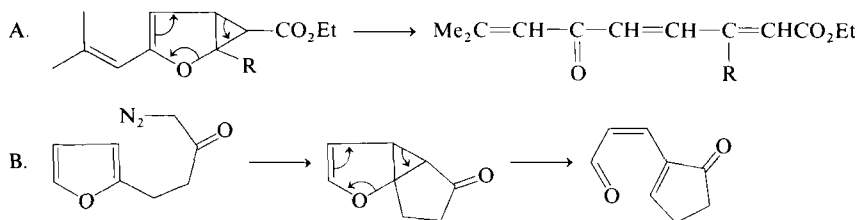
The thermal generation of aryl radicals from acylarylnitrosamines in benzene shows similar anomalous features. There is no 3-arylation of 2,5-dimethylfuran; instead, the 2-methyl group is arylated to a benzyl group. At the same time there may be both azo coupling at the 3-position and a ring opening (perhaps via a cycloaddition product of type **104**). In explanation, Cadogan *et al.*²⁶⁸ suggest that, since 2,5-dimethylfuran is relatively strongly basic, a charge transfer complex might be significant, and that acetate ion (a strong base in nonprotic media) might then be expected to abstract a proton from the now electron-deficient furan nucleus, as in diagram **105**.



²⁶⁸ J. I. L. Cadogan, M. J. P. Harger, J. R. Mitchell, and J. T. Sharp, *J. C. S. Chem. Commun.*, 1432 (1971); J. I. L. Cadogan, J. R. Mitchell, and J. T. Sharp, *J. C. S. Perkin I*, 1304 (1972).

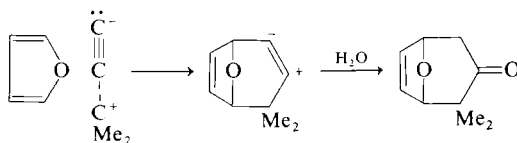
B. CARBENES

Carbenes such as chlorophenylcarbene react preferentially with the alkene group in vinylfurans, the products being furylcyclopropane derivatives.²⁶⁹ Attack by a carbene upon the furan ring itself is, however, also common; and it usually leads to cyclopropane derivatives that undergo ring opening with loss of furanoid character. For instance, steric hindrance is thought to direct attack by $\text{:CHCO}_2\text{Et}$ to the unsubstituted side of 2-isobutenyl-furan giving (presumably) a cyclopropane that collapses to an acyclic ketone (Scheme 51, A).²⁶⁹ The corresponding internal attack by a carbenic center is provoked by treating a furyldiazoketone with CuSO_4 and results in an aldehyde (Scheme 51, B).²⁷⁰ Other instances are known,²⁷¹ and in one case the intermediate cyclopropane could be isolated although it collapsed at 40°C into an aldehyde.²⁷²



SCHEME 51

An interesting variation appears when furan reacts with the allenic carbene generated by the action of potassium *ter*-butoxide upon 1-bromo-3,3-dimethylallene. Though the yield is only 9%, one product is reasonably assigned a structure (Scheme 52) that could hardly be approached by way of a cyclopropane intermediate. The authors comment that in an allenic carbene in the singlet state two electrons will be accommodated in the *sp*



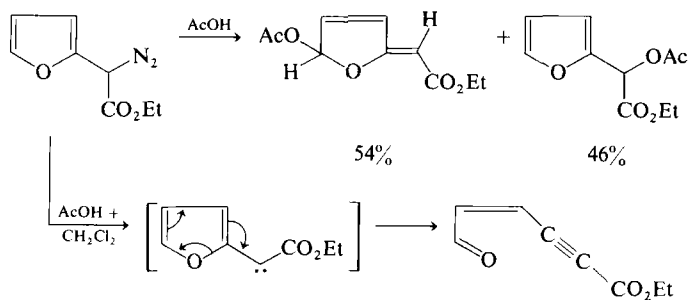
SCHEME 52

²⁶⁹ O. M. Nefedov, V. M. Shostakovskii, and M. I. Kravchenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 379 (1976); O. M. Nefedov, V. M. Shostakovskii, and A. E. Vasilvizky, *Angew. Chem., Int. Ed. Engl.* **16**, 646 (1977).

²⁷⁰ M. N. Nwaji and O. S. Onyiriuka, *Tetrahedron Lett.*, 2255 (1974).

²⁷¹ C. Cauquis, B. Divisa, M. Rastoldo, and G. Reverdy, *Bull. Soc. Chim. Fr.*, 3022 (1971).

²⁷² M. Franck-Neumann and C. Dietrich-Buchecker, *Tetrahedron* **34**, 2797 (1978).



SCHEME 53

orbital while the carbonium center is stabilized by linear delocalization as shown, and they favor formulating the reaction as a concerted ionic cycloaddition leading to a carbenium ion which reacts with water in the final stage.²⁷³

Atomic carbon is generated by thermolysis of diazotetrazole. Whether it should be regarded as a carbene may be a moot point but there seems little doubt that it inserts into furan giving a carbene intermediate.²⁷⁴ Usually atomic carbon attacks ethers by abstracting the oxygen atom (as CO) leaving the residue as two radicals, yet the main product from furan is the acetylenic aldehyde $\text{CH}\equiv\text{CCH}=\text{CHCH}=\text{O}$ which would arise as indicated in **106a**. This collapse correctly places the inserted carbon, as has been demonstrated by using ^{13}C enriched tetrazole to label the starred site. Furan contrasts with most ethers in that in its HOMO there is no electron density on oxygen so carbenes do not attack at that point; methylene, for example, attacks the oxygen in the tetrahydrofuran but the CH or the double bonds in furan. 2-Furylcarbenes never achieve stabilization by ring expansion in the way that benzylic carbenes do; instead, they become acyclic by opening the ring. Generated from furyldiazomethane derivatives, 2-furylcarbenes can be detected by trapping them with alkenes but the main product is always an acetylenic carbonyl compound containing a Z-alkene link formed as outlined in diagram **106b**. The yields are good and the method of synthetic value.²⁷⁵

Unexpectedly, some diazoesters seem to react by way of carbene intermediates even in highly ionic media at room temperature.²⁷⁶ With acetic acid alone 2-furyldiazoacetic ester supplies two products retaining the furan ring. But if the acetic acid is mixed with ether or dichloromethane then a Z-alkenyne (Scheme 53) appears just as if a carbene had been formed. The

²⁷³ S. R. Landon, V. Rogers, and H. R. Sood, *Tetrahedron* **33**, 73 (1977).

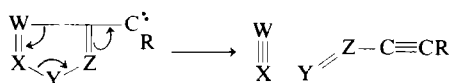
²⁷⁴ S. F. Dyer and P. B. Shevlin, *J. Am. Chem. Soc.* **101**, 1303 (1979).

²⁷⁵ R. V. Hoffman, G. G. Orphanides, and H. Schechter, *J. Am. Chem. Soc.* **100**, 7927 (1978).

²⁷⁶ R. V. Hoffman and H. Shechter, *J. Am. Chem. Soc.* **100**, 7934 (1978).

course of reaction is also affected by which of the metals, copper or mercury, is used, a difference that may be determined by varying modes of coordination. Photolysis of the diazoester in methanol gives all types of products, leading to the view that the central intermediate is a singlet carbene that is partitioned by competing carbenic and ionic processes.

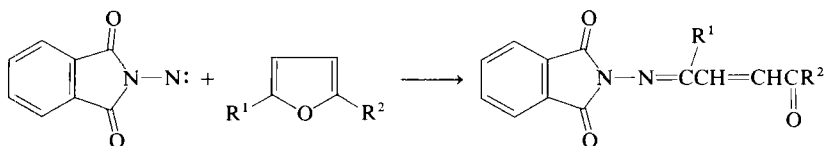
3-Furylcarbenes do not undergo ring opening, and are easily trapped by alkenes or inserted into ethers so that reaction with benzene followed by hydrogenation is a way of making 3-cycloheptylfuran derivatives.²⁷⁷ If they are not trapped they dimerize giving stereoisomeric difurylethylenes.²⁷⁵ Gilchrist and Pearson²⁷⁷ note that the generalized fission occurs only if



W=X is N=N or C=N, never if it is C=C. The ring stability of 3-furylcarbenes conforms with this rule. Ring opening is again the main reaction in a biradical which is generated by extruding carbon dioxide from a lactone at 675°C and which then collapses to an acetylenic ketone.²⁷⁷

C. NITRENES

Azidofurans lose nitrogen giving products reminiscent of those formed from furyl carbenes and biradicals.²⁷⁸ External nitrenes apparently add to furan double bonds just as carbenes do, and again the initial products collapse very readily to give nonheterocyclic products. The nitrene produced oxidation of *N*-aminophthalimide reacts as in Scheme 54. The products are relatively stable derivatives of but-2-enedial and are therefore of potential synthetic value, initially the butene link is *Z* but easily isomerizes to *E* on silica columns.²⁷⁹



SCHEME 54

²⁷⁷ T. L. Gilchrist and D. P. J. Pearson, *J. C. S. Perkin I*, 1257 (1976).

²⁷⁸ S. Gronowita, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B29**, 224 (1975).

²⁷⁹ D. W. Jones, *J. C. S. Perkin I*, 2728 (1972).

Internal nitrenes normally react at the adjacent position. Reduction of 2-(2-nitrophenyl)furan by ethyl phosphite yields furoindole derivatives in fair yield (34%) only, whereas much better results attend the pyrolysis of 2-(2-azidophenyl)furan.²⁸⁰ Furopyrazoles are obtained similarly.²⁸¹ Azidofurans yield nitrenes that insert into adjacent CH links to form furo-pyrroles.²⁸² Quite different results attend either the pyrolysis or the photolysis of azide **107a** for the expected insertion into the side chain occurs giving the related indole but it is accompanied by the surprising replacement of furan oxygen by nitrogen producing **107b** and similar products.²⁸³

D. SILYLENES

With silicon analogues ring fission again provides the dominating feature of external attack. The methoxymethylsilylene MeOSiMe generated by thermolysis of tetramethoxydimethyldisilane converts 2,5-dimethylfuran initially into an adduct that might have provided dimethylcyclobutadiene but actually gave a cyclic siloxene instead. This compound has a special interest as it could be antiaromatic in the Möbius sense; but the UV absorption reveals no such feature.²⁸⁴

VI. Oxidation and Reduction

A. ELECTROCHEMICAL PROCESSES

1. Oxidation

The anodic oxidation of furans has been studied from both synthetic and theoretical points.²⁸⁵ Because of the many possibilities for delocalization, tetraphenylfuran is a special case but it does allow certain basic processes to be monitored by cyclic voltammetry.²⁸⁶ In nitrobenzene two steps are seen;

²⁸⁰ K. Yakushijin and S. Yoshina, *J. Heterocycl. Chem.* **14**, 975 (1977).

²⁸¹ A. Krutosikova, J. Kovac, and J. Kristofcak, *Collect. Czech. Chem. Commun.* **44**, 1799 (1979).

²⁸² S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Acta Chem. Scand., Ser. B* **B30**, 391 (1976).

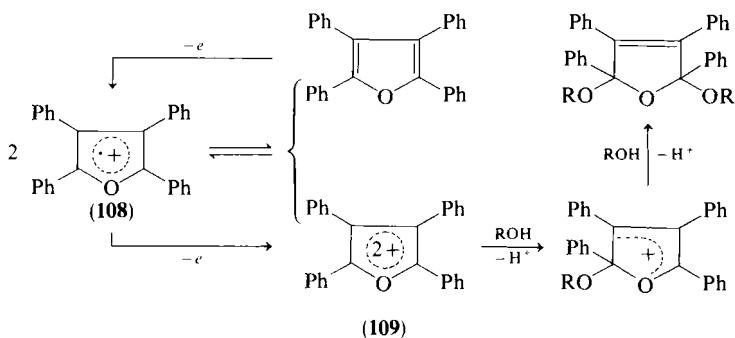
²⁸³ K. Yabushiju, T. Tsuruta, and H. Furukawa, *Heterocycles* **12**, 1021 (1975).

²⁸⁴ M. E. Childs and W. P. Weber, *J. Org. Chem.* **41**, 1799 (1976).

²⁸⁵ N. L. Weinberg and H. R. Weinberg, *Chem. Rev.* **68**, 449 (1968); M. Janda and M. Nemecek, *Chem. Listy* **66**, 225 (1972); M. Ya. Fioshin, L. A. Mirkind, and M. Zh. Zhurinov, *Russ. Chem. Rev. (Engl. Transl.)* **42**, 293 (1973).

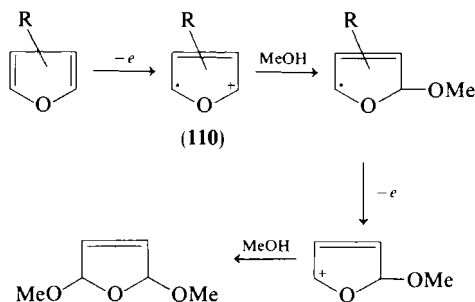
²⁸⁶ M. Libert and C. Caullet, *Bull. Soc. Chim. Fr.*, 805 (1974).

the first removes one electron leaving a cation radical (108), the second removes another leaving the dication 109 which can unusually be isolated as the perchlorate salt. Dismutation of the cation radical (Scheme 55) places this in equilibrium with the dication and with the parent furan. The dication reacts with water or methanol to give a 2,5-dimethoxydihydrofuran derivative. If acids are not removed by insoluble bases then only one faraday is consumed and the cation radical couples with itself giving oligomers and complicating the voltammetric results.



SCHEME 55

In many furans the dicationic state is probably much less easily reached, and it is usual to regard anodic oxidations as ECEC sequences. Thus one electron is removed and cation radical 110 reacts with a nucleophile (methanol, for example). The radical center can lose another electron and then react with another methanol molecule giving the product (Scheme 56).²⁸⁷⁻²⁸⁹ Thus the net result is usually the same as in Scheme (55).



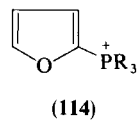
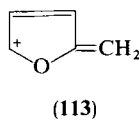
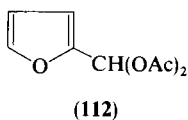
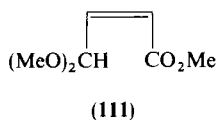
SCHEME 56

²⁸⁷ S. Torii, H. Tanaka, and T. Okamoto, *Bull. Chem. Soc. Jpn.* **45**, 2783 (1972).

²⁸⁸ K. Yoshida, *J. C. S. Chem. Commun.*, 20 (1978); *J. Am. Chem. Soc.* **98**, 254 (1976).

²⁸⁹ A. J. Baggeley and R. Brett, *J. Chem. Soc. C*, 969 (1968).

The electrochemical oxidation is often more sensitive to the reaction conditions than to the substituents. Platinum electrodes are recommended for methoxylation and the equivalent acetoxylation procedures.²⁹⁰ In acetonitrile buffered by hydrogen carbonate ion, 3,4-diethylfuran affords the 2,5-dihydroxy-2,5-dihydro derivative (84%) and Jones' oxidation readily leads to diethylmaleic anhydride in what is claimed to be the best general method for such conversions.²⁹¹ In unbuffered methanol and under current density control, the oxidation of 2-methylfuran appears to eliminate the methyl group since the product is the acetal-ester **111** also obtained from methyl 2-furoate.²⁹² If sodium acetate buffer is used, however, the methyl group is retained but oxidized in part to the aldehyde diacetate **112** in a



reaction strongly resembling an oxidation by lead(IV) salts.²⁸⁹ It appears that if the dication oxidation state as in **109** is achieved without adequate delocalization then one proton has to be ejected giving the exomethylenic cation **113**. This adds acetic acid at the methylene terminus, and repetition affords the diacetate. In methanol containing cyanide ion the addition of methanol at the terminal methylene leads to the methoxymethylfuran series in a similar manner.²⁹³

Yoshida has studied anodic oxidations in methanol containing cyanide to elucidate the electrode processes themselves.²⁸⁸ He finds that, under controlled potential (~ 1.2 V), 2,5-dimethylfuran gives a methoxynitrile as well as a dimethoxy compound (Scheme 57). Cyanide competes for the primary cation radical but not for the secondary cations so that the product always contains at least one methoxy group. On a platinum electrode the cis-trans ratio in the methoxynitrile fraction is affected by the substrate concentration and by the addition of aromatic substances suggesting that adsorption on the electrode helps determine the stereochemistry. On a vitreous carbon electrode, which does not strongly adsorb aromatic species, the ratio always approaches the equilibrium value.

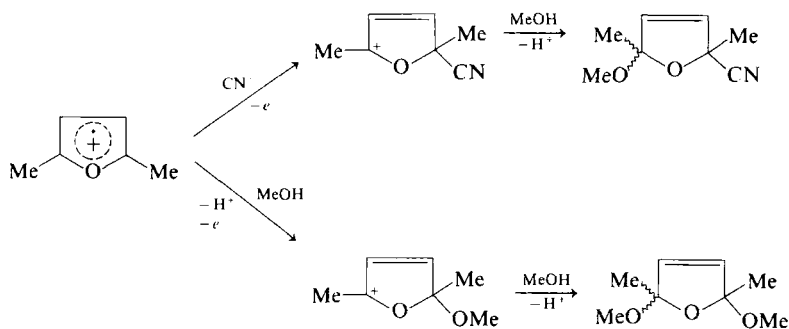
An alternative reaction mode may be encountered in which the primary cation radical picks up a nucleophile but then loses an electron and a proton to regain the aromatic furan state. Such processes simulate substitution

²⁹⁰ J. Froberg, C. Magnusson, and S. Thoren, *J. Org. Chem.* **40**, 122 (1975).

²⁹¹ K. E. Kolb and C. L. Wilson, *J. C. S. Chem. Commun.*, 271 (1966).

²⁹² H. Tanaka, Y. Kobayasi, and S. Torii, *J. Org. Chem.* **41**, 3482 (1976).

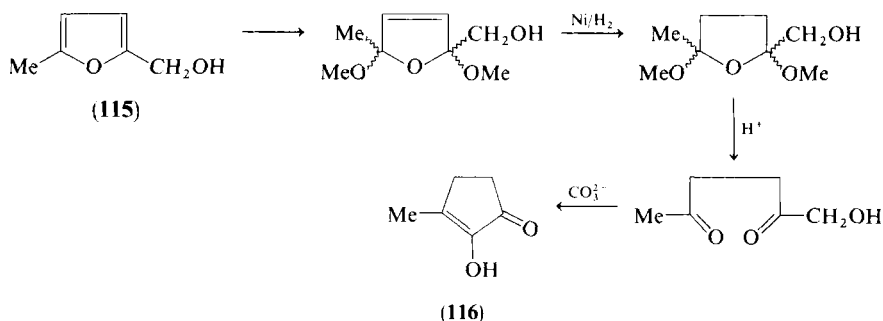
²⁹³ K. Yoshida and T. Fueno, *J. Org. Chem.* **36**, 1523 (1971).



SCHEME 57

reactions and are better conducted in solvents such as acetonitrile than in methanol. An example is the oxidation at platinum of furan in the presence of a phosphine to give a furylphosphonium salt **114**.²⁹⁴

For synthetic purposes the prime oxidation is that leading to 2,5-dihydroxy-dihydrofuran derivatives as in Schemes 55 and 56. Thus 5-methylfurfuryl alcohol **115** can be transformed in stages outlined in Scheme 58a to the cyclopentenone **116** which is an important substance affecting the flavor of



SCHEME 58a

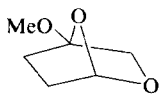
several major foods.²⁹⁵ For reasons noted above, there is often a preponderance of the *cis*-dimethoxy intermediates, and there is in addition a tendency for acyl substituents to be converted into their acetals.²⁹⁶ Furan-2-carbaldehyde, however, affords only the bicyclic product **117**.²⁹⁵

²⁹⁴ E. V. Nikitin, Yu. M. Kargin, O. V. Parakin, A. N. Pudovic, and G. V. Romanov, U.S.S.R. Patent 652,186 [CA 20711 (1979)].

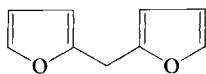
²⁹⁵ T. Shono, Y. Matsumura, and H. Hamaguchi, *J. C. S. Chem. Commun.*, 712 (1977).

²⁹⁶ J. Srogl, M. Janda, and I. Stibor, *Collect. Czech. Chem. Commun.* **38**, 3666 (1973); O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzschowska, and A. Zamojski, *Tetrahedron* **27**, 1973 (1971).

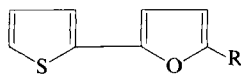
²⁹⁷ J. Srogl, M. Janda, I. Stibor, and Z. Salajka, *Collect. Czech Chem. Commun.* **42**, 1361 (1977).



(117)



(118)

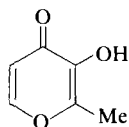


(119) R = H

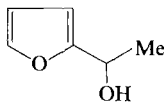
(120) R = OMe

Also as noted above any substituents present have little effect upon such oxidations. In 2,2'-methylenebisfuran (118) the rings are attacked simultaneously giving a tetramethoxy derivative.²⁹⁷ Even the bulk of the *tert*-butyl group has little effect.²⁹⁸ The only marked substituent effect is that exerted by an aromatic (benzene, thiophene, furan) residue which, if directly attached at the 2-position, promotes elimination instead of the addition of another methoxy group. The net process then becomes one of arylation, as when 2-(2-thienyl)furan (119) is oxidized to 120.²⁹⁸ There are reports that acetyl and carboxy groups can be ejected during oxidation, but that ester groups are usually retained.²⁸⁷

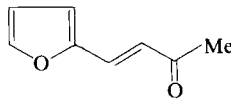
Anodic hydroxylation/methoxylation of furans has an exact chemical counterpart in the well-known bromine/methanol reaction, and the choice of method is not always easily made. One can compare the two methods particularly easily in syntheses of the flavoring component, the pyrone maltol 121, from the furan 122 since one group used the electrolytic method²⁹⁹ and another the chemical method.³⁰⁰



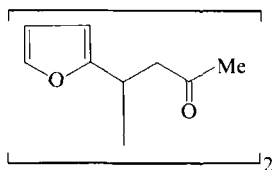
(121)



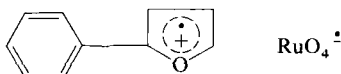
(122)



(123)



(124)



(125)

²⁹⁸ I. Stibor, J. Srogl, and M. Janda, *J. C. S. Chem. Commun.*, 397 (1975).

²⁹⁹ T. Shono and Y. Matsumura, *Tetrahedron Lett.*, 1363 (1976).

³⁰⁰ T. M. Brennan, P. D. Weeks, D. P. Brannegan, D. E. Kuhla, M. L. Elliott, H. A. Watson, and B. Wlodecki, *Tetrahedron Lett.*, 331 (1978).

2. Reduction

Studies of cathodic reduction have been few. Amusingly, attempted anodic oxidation of the furyl ketone **123** actually resulted in cathodic reduction to the dimer **124**; the corresponding ester was oxidized normally, however.³⁰¹ Sometimes the dimethoxydihydrofurans formed in oxidation processes are reduced in a side reaction leading to the tetrahydrofuran derivatives.³⁰² By using dimethylformamide as solvent instead of the protic solvents used formerly, a Czech group has demonstrated that the cathodic reductions of furans can produce fairly stable anion radicals having ESR spectra which agree well with theory.^{302a}

B. CHEMICAL PROCESSES

1. Oxidation

Since furans are "electron rich" compounds it is probable that many oxidations proceed by an initial loss of one electron to give a cation radical intermediate as, in fact, is commonly proposed for anodic oxidations. Most of the evidence is indirect and so the observations made by Ayres and Gopalan are particularly interesting; they found that ruthenium tetroxide converts 2-arylfurans into cation radicals that can be studied since they form fairly stable, purple charge-transfer complexes **125** with the reagent.³⁰³ The benzenoid protons show a 50 Hz downfield shift and the complex provides a broad signal with g 2.0036. Oxidative destruction of the furan ring by chlorate(I) in the presence of ruthenium tetroxide bears many of the characteristics of radical reactions,³⁰³ and the benzoyl peroxide oxidations mentioned in Section V,A have been interpreted by means of cation radical intermediates.³⁰⁴

Electrochemical oxidations at an electron-deficient platinum electrode have considerable resemblance to oxidations by lead(IV) salts or halogens in methanol but none whatever to oxidations by palladium(II) salts. At temperatures between 90 and 130°C in solution these smoothly convert

³⁰¹ H. Santonaka, Z. Saito, and T. Shimura, *Bull. Chem. Soc. Jpn.* **46**, 2892 (1973).

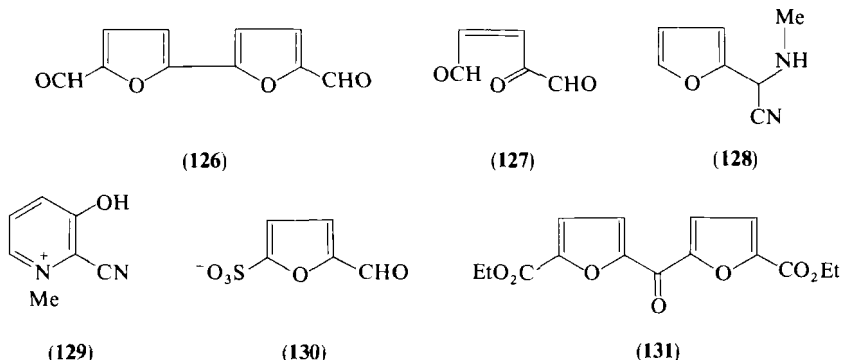
³⁰² J. Srogl, M. Janda, J. Hajkova, and U. Kubelka, *Collect. Czech. Chem. Commun.* **35**, 3462 (1970).

^{302a} A. Stasko, P. Pelikan, F. Tomanovic, and V. Patoprsty, *Collect. Czech. Chem. Commun.* **44**, 762 (1979).

³⁰³ D. C. Ayres and R. Gopalan, *J. C. S. Chem. Commun.*, 890 (1976).

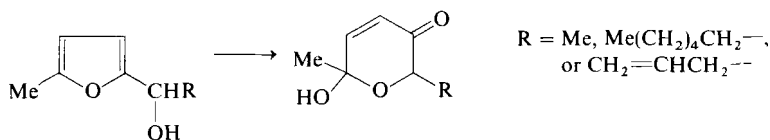
³⁰⁴ D. C. Nonhebel and J. C. Walton, "Free Radical Chemistry," p. 446. Cambridge Univ. Press, London and New York, 1947.

simple 2-substituted furans into derivatives of 2,2'-difuran including the parent compound and the useful dialdehyde **126**.³⁰⁵ A mixture of furan and thiophene yields the thienylfuran **119**. Chemical hydroxylation by means of



halogens in water or methanol is still much used; the product from furfural corresponds to the synthon dialdehyde **127** from which aminopyridines and pyridones are readily available.³⁰⁶ An elegant development is the intramolecular equivalent where, for example, **128** affords **129** in one step.³⁰⁷ Additionally the synthon **127** reacts with sodium hydrogen sulfite to provide a remarkably smooth preparation of the furfural sulfonate **130**.³⁰⁸ Related oxidations supply flavoring agents, prostaglandin and cephalosporin intermediates and other useful materials.^{296,300,309,309a} The hydroxylation of 3-substituted furans to reach branched-chain sugars is particularly attractive.²⁹⁶

The newer reagent, pyridinium chlorochromate(VI), has the particular (though not unique) ability to transform furylcarbinols into pyran derivatives under remarkably mild conditions (dichloromethane at room temperature for 1 h).³¹⁰ The conversion shown in Scheme 58b exemplifies the general



SCHEME 58b

³⁰⁵ I. V. Kozhevnikov, *React. Kinet. Catal. Lett.* **4**, 851 (1976); **5**, 415 (1976).

³⁰⁶ H. Greuter and T. Winkler, *Helv. Chim. Acta* **61**, 3103 (1978).

³⁰⁷ J. B. Petersen, K. Norris, N. Clauson-Kaas and K. Svanholt, *Acta Chem. Scand.* **23**, 1785 (1967).

³⁰⁸ G. Jansen, J. Lei, and N. Clauson-Kaas, *Acta Chem. Scand.* **25**, 340 (1971).

³⁰⁹ J. A. Edwards, A. Guzman, R. Johnson, P. J. Seeby, and J. H. Fried, *Tetrahedron Lett.*, 2031 (1974); B. T. Gillis and J. C. Valentour, *J. Heterocycl. Chem.* **8**, 13 (1971).

^{309a} L. Bassignani, A. Brandt, V. Caciagli, and L. Re, *J. Org. Chem.* **43**, 4245 (1978).

³¹⁰ G. Piancatelli, A. Scettri, and M. D'Auria, *Tetrahedron Lett.*, 2199 (1977); 1507 (1979).

method and also demonstrates that a secondary alcohol can survive the treatment even though the reagent was originally introduced as an oxidant for alcohols. Nor is the alcohol group attacked in the useful variant in which 5-bromo-2-furylcarbinols are oxidized to butenolides in yields up to 75%.³¹⁰ Anodic oxidation can also be used for the oxidative removal of bromine.²⁸⁷ In contrast, chromium(VI) oxide attacks only the central methylene group in compounds like **118** and leaves the furan rings intact as in a preparation of the diester **131**.³¹¹ Of course, the rings are protected to some extent by the electronegative ester substituents, but even without such protection the oxidation of the furan ring may still take several days.³¹² The furan ring also withstands cerium(IV) salts, at least in the oxidation of furoin to furoic acid.³¹³ And silver oxide is still the prime oxidant for converting furan aldehydes into acids even when used catalytically with oxygen on a large scale.³¹⁴ There are cobalt-manganese catalysts that promote the oxidation by air of nuclear methyl groups,³¹⁵ and other catalysts that promote oxidation of the ring itself.³¹⁶

Attempts to oxidize furans with tetrachloro-1,2-benzoquinone (*o*-chloranil) result in cycloadditions yielding dioxane derivatives instead, e.g., from ethyl 3-(2-furyl)propenoate.³¹⁷ Since oxidations by perphthalic acid and related reagents are slow they are seldom a nuisance when oxidation is required at another site³¹⁸ and can be an asset as in the conversion of the oestrone derivative **132** into the hydroxypyranone **133**.³¹⁹ Soviet workers find that hydrogen peroxide at -15°C slowly adds to furfural to give the hydroxyhydroperoxide **134** in very high yield; there is almost no oxidation of the ring or of the aldehyde group.³²⁰ However, hydrogen peroxide does oxidize furan to a butenolide if selenium dioxide is present; kinetic studies show that a selenium peroxy acid is formed first and effects the oxidation.³²¹ The conversion of the furan analogue **135** of a chalcone into the "chalcone epoxide" is better achieved with chlorate(I) in dichloromethane and an acid catalyst

³¹¹ S. Pennanen, *Acta Chem. Scand.*, **26**, 1961 (1972).

³¹² M. S. Henderson, R. McCrindle, and D. McMaster, *Can. J. Chem.*, **51**, 1346 (1973).

³¹³ T.-L. Ho, *Synthesis*, 560 (1972).

³¹⁴ V. A. Slavinskaya, D. Kreile, D. Sile, D. Eglite, and L. Ya. Kruminya, *React. Kinet. Catal. Lett.*, **11**, 215 (1979).

³¹⁵ E. Dziluma, S. Hillers, V. A. Slavinskaya, V. M. Evgrashin, D. Kreile, A. Strautina, and I. A. Mil'man, *Prep. Catal., Proc. Int. Symp.*, 1975, 187 (1976).

³¹⁶ I. G. Iovel and M. V. Shimanskaya, *React. Kinet. Catal. Lett.*, **12**, 171 (1979).

³¹⁷ N. Latif, N. S. Girgis, and F. Michael, *Tetrahedron*, **26**, 5765 (1970).

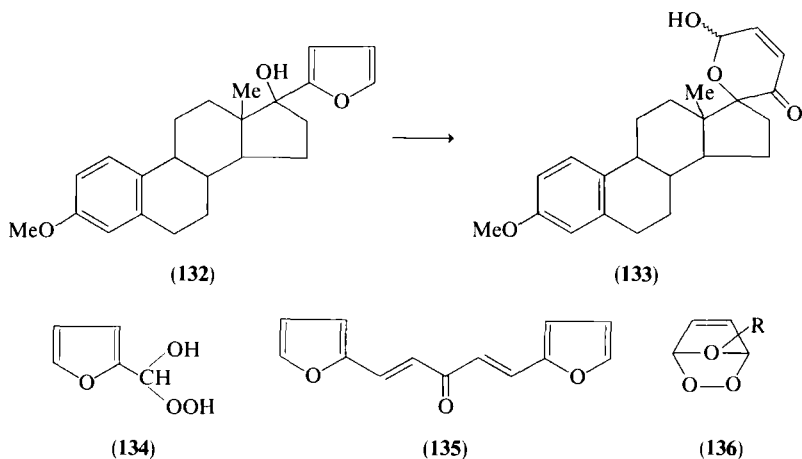
³¹⁸ L. Mangoni, M. Adinolfi, G. Laonigro, and R. Caputo, *Tetrahedron*, **28**, 611 (1972); D. Lavie and E. C. Levy, *Tetrahedron Lett.*, 1315 (1970).

³¹⁹ Y. Lefebvre, *Tetrahedron Lett.*, 133 (1972).

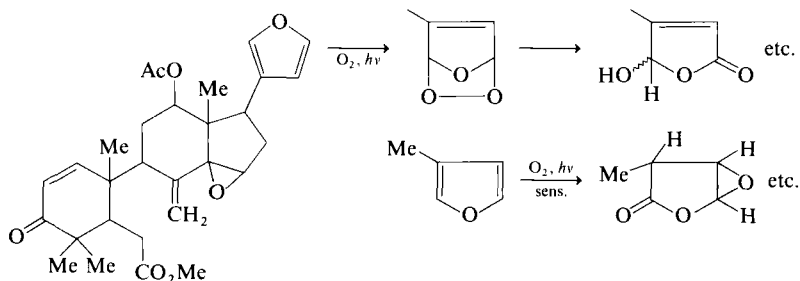
³²⁰ L. A. Badovskaya, G. D. Krapinin, T. Ya. Kaklyugina, V. G. Kul'nevich, and G. F. Muzychenko, *Zh. Org. Khim.*, **11**, 1446 (1975).

³²¹ S. P. Gavrilova, L. A. Badovskaya, and V. G. Kul'nevich, *Kinet. Katal.*, **20**, 1338 (1979).

(tetrabutylammonium hydrogen sulfate) in phase transfer conditions than with the conventional alkaline hydrogen peroxide.³²²



The catalyzed oxidations of furan were considered above, and the reactions of furyllithium with oxygen in Section IV,A,1. There remains the addition of singlet oxygen. Furans add singlet oxygen in what appears to be a concerted cycloaddition reaction and products, **136** can be regarded as the ozonides of cyclobutadiene derivatives. This could well be the only case where an ozonide was known before the parent alkene. The cycloaddition mechanism has been questioned and the interesting observation has been made that the addition rate is independent of temperature indicating a reaction that is controlled purely by entropy factors.³²³ While studying the chemistry of toonacinil, a



SCHEME 59

³²² A. Arcoria, F. P. Ballistreri, A. Cantone, G. Masumarra, and M. Tripolone, *Gazz. Chim. Ital.* **110**, 267 (1980).

³²³ A. A. Gorman, G. Lovering, and M. A. T. Rodgers, *J. Am. Chem. Soc.* **101**, 3050 (1979).

highly oxidized terpenoid furan found in *Toona ciliata*, Grimmering and Kraus found that in aprotic solvents the photochemically induced oxidations take different forms depending upon the presence or absence of a sensitizer (methylene blue). With no sensitizer the usual bridged intermediate **136** was formed and collapsed into a mixture of butenolides, a form of reaction already well known. In the absence of a sensitizer a new reaction was noted in which lactonic epoxides were predominant (Scheme 59).³²⁴

2. Reduction

The catalytic hydrogenation of furan and its derivatives has been the subject of determined and extensive study in eastern European countries and the Soviet Union, so that considerable control over the results is now possible. An iron-promoted cobalt catalyst is extremely selective for reducing furfural to furanmethanol,³²⁵ whereas the conventional Raney nickel catalyst saturates difurfurylideneacetone **135** first at the alkene links, then at the furan rings, and only finally at the carbonyl group.³²⁶ Although the saturation of the furan nucleus is usually slow enough for external alkene bonds to be selectively saturated, care is needed if the alkene is conjugated with the furan nucleus.³²⁷ In conjugated systems ammonia may confine the reduction to the alkene if the catalyst is nickel.^{327a} Nickel catalysts have also been found to give higher yields of cis-disubstituted tetrahydrofurans where palladium and other catalysts gave mixtures of stereoisomers.³²⁸ In a synthesis of nonactin the furan ring was reduced by means of a rhodium catalyst,³²⁹ to give preponderantly cis products without breaking any ether links, but under extreme conditions rhodium catalysts induce the nucleus to collapse into ketonic fragments such as acetone and 2-pentanone.³³⁰

For selective reduction of the unreactive double bond in the acid **137** from a species of *Dodonaea*, Payne and Jeffries³³¹ preferred to use diimide as

³²⁴ W. Grimmering and W. Kraus, *Justus Liebigs Ann. Chem.*, 1571 (1979).

³²⁵ M. S. Erzhanova, T. Beisekov, and E. Elemesov, *Teor. Osn. Pererab. Miner. Org. Syr'ya* **3**, 153 (1976) [*CA* **91**, 56726 (1979)].

³²⁶ R. Mat'yakubov, Yu. M. Mamatov, N. Kh. Mukhamadaliyev, and E. G. Abduganiev, *Khim. Geterotsikl. Soedin.*, 462 (1979).

³²⁷ M. Bartok, K. Lakos-Lang, L. G. Bogatskaya, G. L. Kamalov, and A. V. Bogatskii, *Dokl. Akad. Nauk SSSR* **234**, 590 (1977) [*CA* **87**, 102098].

^{327a} M. B. Floyd, *J. Org. Chem.* **43**, 1641 (1978).

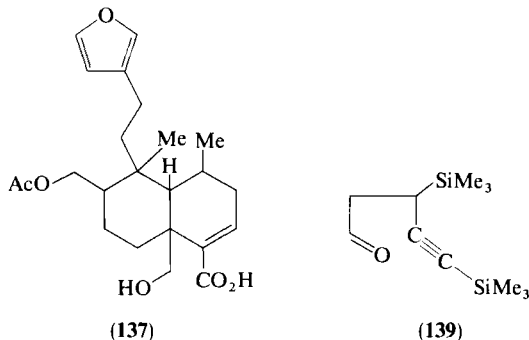
³²⁸ M. L. Mihailovic, R. I. Mamuzic, L. Zigic-Mamuzic, J. Bosnjak, and Z. Cekovic, *Tetrahedron* **23**, 215 (1967).

³²⁹ U. Schmidt, J. Gombos, E. Haslinger, and H. Zak, *Chem. Ber.* **109**, 2628 (1976).

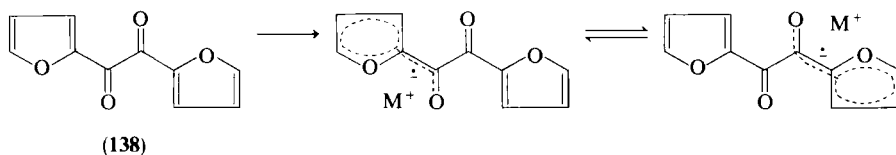
³³⁰ B. B. Blinov, S. A. Eigenson, O. S. Korneva, A. A. Nazaryan, M. V. Vagabov, R. A. Karakhanov, and K. G. Danelyan, *Zh. Prikl. Khim. (Leningrad)* **52**, 2071 (1979).

³³¹ T. G. Payne and P. R. Jeffries, *Tetrahedron* **29**, 2575 (1973).

recommended by Eugster and his colleagues.³³² Another useful method of adding hydrogen is the so-called ionic hydrogenation with triethylsilane in trifluoroacetic acid; 2-methylfuran is reduced to 2-methyltetrahydrofuran, and 2-acetylfuran to 2-ethyltetrahydrofuran.³³³ A large excess of the reagent is used, but the reaction time is of the order of a few minutes and the yields are high. No doubt the method could be greatly extended.



Reduction of furan compounds by alkali metals, although important, has not been subjected to physical and mechanistic studies, except for the electrochemical equivalent mentioned above^{302a} and the somewhat tangential case of furil (138) which has been shown to accept one electron and to form both ion pairs (M^+ furil⁻) and triple ions ($2M^+$ furil⁻). The cation is tightly held by the oxygen atoms and does not move easily from one to another, equivalent site (Scheme 60) so the ESR signals are sharp and give good hyperfine coupling constants.³³⁴ Further addition of electrons from alkali metals destroys the furan ring. A synthetically valuable reaction is described by Kuwajima and his colleagues who use sodium to supply electrons and trap the products with trimethylsilyl chloride. For example, the acetylenic aldehyde 139 is easily obtained from ethyl 2-furoate.³³⁵



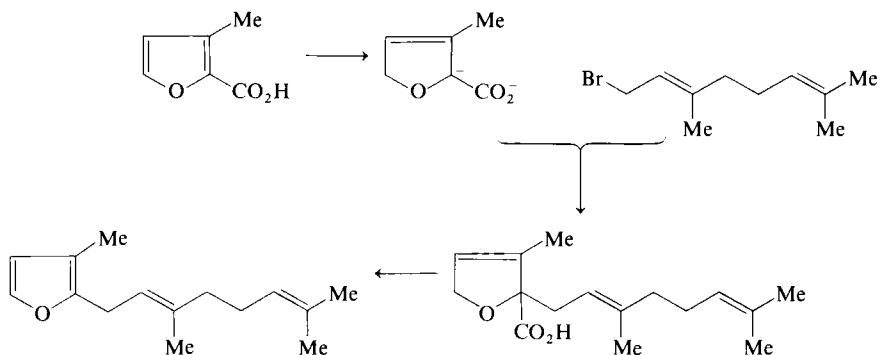
SCHEME 60

³³² J. S. Scarpa, M. Ribi, and C. H. Eugster, *Helv. Chim. Acta* **49**, 858 (1966).

³³³ G. I. Bolestova, Z. N. Parnes, and D. N. Kursanov, *Zh. Org. Khim.* **15**, 1264 (1979).

³³⁴ K. S. Chen and J. K. S. Wan, *J. Am. Chem. Soc.* **100**, 6051 (1978).

³³⁵ I. Kuwajima, K. Atsumi, and I. Azagami, *J. C. S. Chem. Commun.*, 76 (1977).



SCHEME 61

Ring opening is also common in reductions under Birch conditions unless some anion-stabilizing group is attached. The carboxyl group is marginally satisfactory and enabled high yields of the 2,5-dihydro acid to be obtained by reducing 2-furoic acid with lithium in ammonia at -78°C provided that quenching was initiated within 3 minutes. Birch and Slobbe created a new way of substituting the furan ring. Reduction of 5-methylfuran-2-carboxylic acid may first give an anion (Scheme 61) which is easily alkylated; the acid so formed is converted back into a true furan (sesquirosefuran in Scheme 61) by oxidative decarboxylation with lead(IV) acetate.³³⁶ Unfortunately, the presence of a phenyl group accentuates ring opening.³³⁷ Ring opening is also the feature of the reduction of 3-furoic acid that allows a recyclization at the carboxy group so that, somewhat unexpectedly, the main products are lactones.³³⁸ However, if the reduction is carried out in the presence of an alcohol ring opening is minimal and good yields of di- or tetrahydrofurans are obtainable.³³⁷⁻³³⁹ In general, alcohols favor the formation of hydrofurans, and if the optically active alcohol, 1,2:5,6-di-*O*-isopropylidene- β -D-glucofuranose, is the proton source, then asymmetric reduction occurs to the extent of about 3%; the absolute configuration remains to be determined.³⁴⁰ The use of amines instead of ammonia is not common; one report states that furan is reduced by an excess of lithium in methylamine to give some butanol and a major amount of the methylimine of butanal.³⁴¹

³³⁶ A. J. Birch and J. Slobbe, *Tetrahedron Lett.*, 627 (1975); 2079 (1976).

³³⁷ T. Masamune, M. Ono, and H. Matsue, *Bull. Chem. Soc. Jpn.*, **48**, 491 (1975).

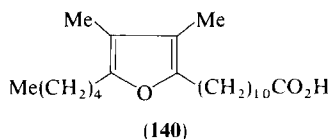
³³⁸ J. Slobbe, *Aust. J. Chem.*, **29**, 2553 (1976).

³³⁹ T. Kinoshita, K. Miyano, and T. Miwa, *Bull. Chem. Soc. Jpn.*, **48**, 1865 (1975).

³⁴⁰ T. Kinoshita and T. Miwa, *J. C. S. Chem. Commun.*, 181 (1974).

³⁴¹ A. O. Bedenbaugh, J. H. Bedenbaugh, J. D. Adkins, and W. A. Bergin, *J. Org. Chem.*, **35**, 543 (1970).

During their work on the furanoid lipids of fish, Rahn *et al.*³⁴² synthesized a number of compounds such as **140** by acylating a furan derivative and reducing the carbonyl to a methylene group by means of the Wolff-Kischner method. Curiously, the Wolff-Kischner reduction usually fails with furyl ketones. Destruction of the ring (vinylogous ester) by the extremely basic medium may often be responsible. The favored routine for removing carbonyl oxygen now seems to be to reduce the ketone to an alcohol which is then esterified, and the ester residue is removed by calcium, sodium, or lithium in ammonia.^{177,224,343,344} Dry distillation of 2,5-dimethylfuran from a mixture of 5-methylfurfural and lithium aluminum hydride³⁴⁵ seems too drastic a measure for general use, but the reduction and hydrolysis of furan nitriles to furan aldehydes is cleanly effected by diisopropylaluminum hydride.³⁴⁶



³⁴² C. H. Rahn, D. M. Sand, Y. Wedmid, H. Schlenk, T. P. Krick, and R. L. Glass, *J. Org. Chem.* **44**, 3420 (1979).

³⁴³ R. A. Bell, M. B. Gravestock, and V. Y. Tuguchi, *Can. J. Chem.* **50**, 3749 (1972).

³⁴⁴ S. Takahashi, T. Kusumi, and H. Kakisawa, *Chem. Lett.*, 515 (1979).

³⁴⁵ T. Severin and I. Ipach, *Synthesis*, 796 (1973).

³⁴⁶ M.-C. Zaluski, M. Robba, and M. Bonhomme, *Bull. Chem. Soc. Fr.*, 1445 (1970).

The Photochemistry of Nitrogen-Containing Heterocycles

S. T. REID

*University Chemical Laboratory, University of Kent at Canterbury, Canterbury,
Kent CT2 7NH, England*

| | |
|---|-----|
| I. Introduction | 239 |
| II. Bond Cleavage and Rearrangement | 240 |
| A. Electrocyclic Reactions | 240 |
| 1. 4π Systems. | 240 |
| 2. 6π Systems. | 243 |
| 3. Nitrones and Heteroaromatic <i>N</i> -Oxides | 248 |
| B. Miscellaneous Reactions | 256 |
| 1. Three- and Four-Membered Heterocycles | 256 |
| 2. Five- and Six-Membered Heterocycles | 265 |
| 3. Medium- and Large-Ring Heterocycles | 276 |
| III. Photoaddition | 278 |
| A. Photocycloaddition to Heterocycles | 278 |
| 1. $[\pi 2 + \pi 2]$ Cycloadditions | 278 |
| 2. $[\pi 4 + \pi 4]$ Cycloadditions | 282 |
| 3. Miscellaneous Cycloadditions | 284 |
| B. Synthesis of Heterocycles by Photoaddition. | 285 |
| C. Photoaddition to Heterocycles | 289 |
| IV. Photocyclization | 292 |
| A. Norrish Type II Cyclizations. | 293 |
| B. Photoelimination of HX | 297 |
| C. Miscellaneous Photocyclizations | 300 |
| V. Photoelimination | 305 |
| A. Photoelimination of Nitrogen | 305 |
| B. Photoelimination of Carbon Dioxide | 316 |

I. Introduction

The study of the photochemistry of heterocyclic systems is a rapidly expanding area of research. Attention has been directed in the literature not only to the photoreactions of such systems but also to the synthesis of new and novel heterocycles by photochemical routes. The subject was

previously reviewed in 1970 in *Advances in Heterocyclic Chemistry*.¹ This review is an attempt to update that earlier review with respect to nitrogen containing heterocycles; a separate review on systems containing oxygen and sulfur will follow. The arrangements employed in this chapter are similar to those adopted previously but are modified in the light of further developments in the subject.

This survey, which covers the period 1969 to June 1980, is intended to be selective rather than comprehensive in its coverage. The field has expanded so rapidly that it would be totally unrealistic to attempt to include all relevant papers. Emphasis will be placed in this article on novel reaction types and on new heterocyclic systems rather than on additional examples of well known transformations.

II. Bond Cleavage and Rearrangement

A. ELECTROCYCLIC REACTIONS

1. 4π Systems

Examples of 4π electrocyclization in 6-, 7-, and 8-membered nitrogen containing cyclodienes to give bicyclic systems have been widely reported. Such processes appear to occur relatively efficiently although in some cases the cyclization is thermally or photochemically reversible. The well-known conversion of pyrid-2-ones to 2-azabicyclo[2.2.0]hex-5-en-3-ones has been extended to a variety of substituted pyrid-2-ones^{2,3} and to pyrimidin-2-ones **1** which on irradiation in benzene are converted to the thermally stable diazabicyclo[2.2.0]hexenes **2**.⁴ The corresponding photoproduct **3** of the pyrazinone **4** is less stable but it has been trapped as the dihydro derivative **5**,³ and the unstable azetine **6** has been identified along with the ketene **7** on irradiation of 1,3-oxazin-6-one **8** in an argon matrix.⁵ Further irradiation of the azetine **6** affords products arising by decarboxylation which are best rationalized in terms of the formation of an intermediate azacyclobutadiene.⁶

¹ S. T. Reid, *Adv. Heterocycl. Chem.* **11**, 1 (1970).

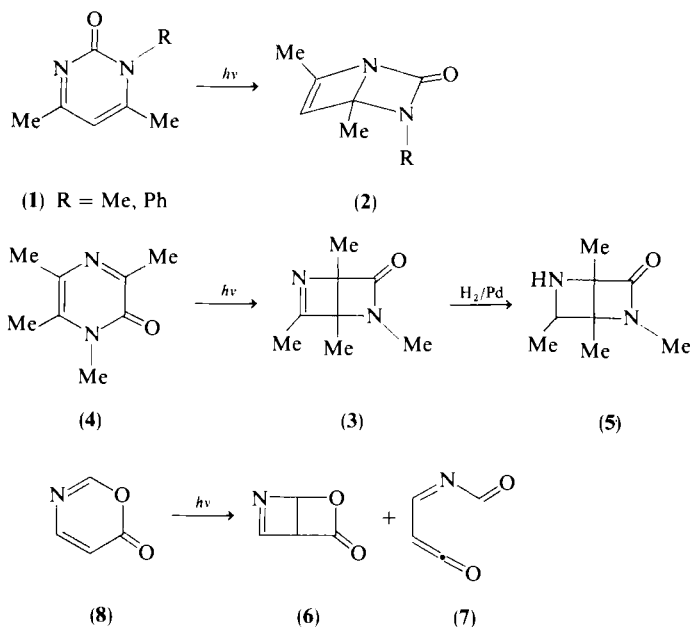
² R. C. De Selms and W. R. Schleigh, *Tetrahedron Lett.*, 3563 (1972); W. L. Dilling, N. B. Tefertiller, and A. B. Mitchell, *Mol. Photochem.* **5**, 371 (1973).

³ H. Farrer, *Chem. Ber.* **105**, 2780 (1972).

⁴ T. Nishio, A. Kato, C. Kashima, and Y. Omote, *J. C. S. Perkin I*, 607 (1980).

⁵ A. Kranz and B. Hoppe, *J. Am. Chem. Soc.* **97**, 6590 (1975).

⁶ G. Maier and U. Schäfer, *Tetrahedron Lett.*, 1053 (1977); *Justus Liebigs Ann. Chem.*, 798 (1980).



Numerous examples of analogous cyclizations have been reported in azepines and diazepines and lead both to carbon-bridged and nitrogen-bridged bicycles. Thus, for example, 1-ethoxycarbonyl-1*H*-azepine (**9**) is converted via the singlet excited state in virtually quantitative yield to the valence isomer **10**.⁷ Similar transformations have been observed in 3*H*-azepines which are converted exclusively to 2-azabicyclo[3.2.0]hepta-2,6-dienes⁸ and in 2,3-dihydro-1*H*-azepines,⁹ 4,5-dihydro-3*H*-azepines,¹⁰ and 1,3-dihydro-2*H*-azepinones.¹¹ 1,2(1*H*)-Diazepines **11** on irradiation give the corresponding diazabicyclo[3.2.0]heptadienes **12**,¹² and similar photocyclizations have been observed in 1,3(1*H*)-diazepines¹³ and in the 1,2(4*H*)-diazepine **13** which affords the thermally unstable 1,2-diazabicyclo[3.2.0]hepta-2,6-diene **14**.¹⁴ Related photoreactions have been reported in 1,3-

⁷ G. Jones and L. J. Turbini, *J. Org. Chem.* **41**, 2362 (1976).

⁸ R. A. Odum and B. Schmall, *J. C. S. Chem. Commun.*, 1299 (1969).

⁹ K. Shudo and T. Okamoto, *Chem. Pharm. Bull.* **22**, 1204 (1974).

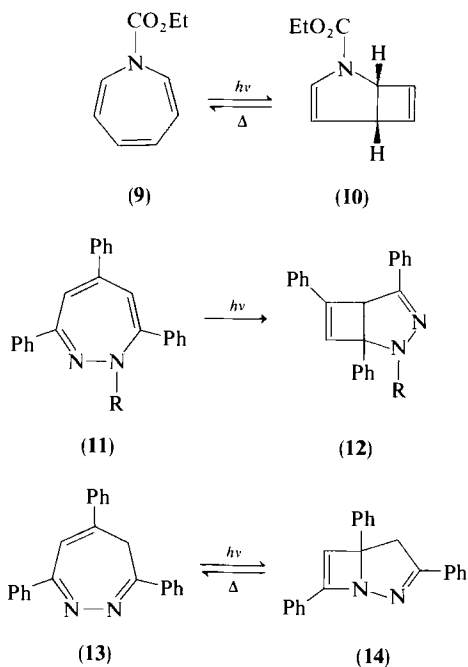
¹⁰ T. H. Koch and D. A. Brown, *J. Org. Chem.* **36**, 1934 (1971); E. Lerner, R. A. Odum, and B. Schmall, *J. C. S. Chem. Commun.*, 327 (1973).

¹¹ J. W. Pavlik and C. A. Seymour, *Tetrahedron Lett.*, 2555 (1977).

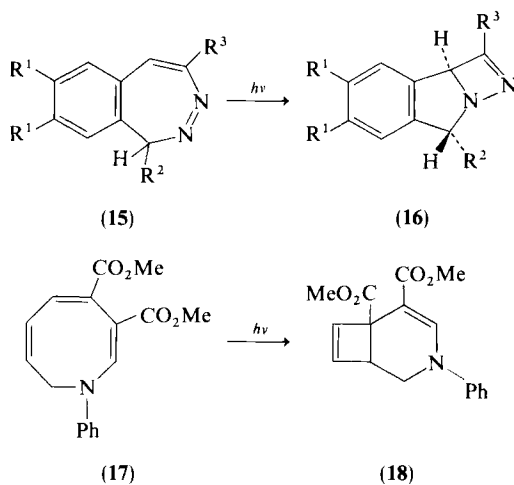
¹² G. Kan, M. T. Thomas, and V. Snieckus, *J. C. S. Chem. Commun.*, 1022 (1971).

¹³ T. Tsuchiya, J. Kurita, and H. Kojima, *J. C. S. Chem. Commun.*, 444 (1980).

¹⁴ D. J. Harris, M. T. Thomas, V. Snieckus, N. Friedman, K. Schaumburg, K. B. Tomer, and O. Buchardt, *Can. J. Chem.* **55**, 56 (1977).



oxazepines¹⁵ and in the benzodiazepines **15** which are converted to the first isolable 1,2-diazetines **16**.¹⁶



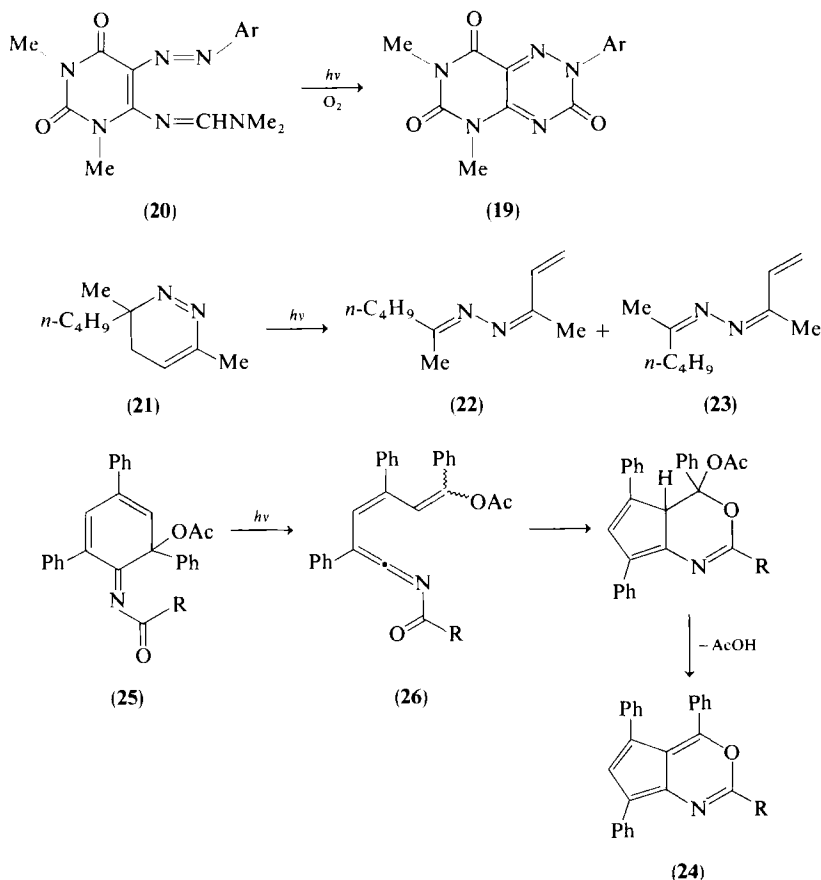
¹⁵ T. Tezuka, O. Seshimoto, and T. Mukai, *J. C. S. Chem. Commun.*, 373 (1974).

¹⁶ A. A. Reid, H. R. Sood, and J. T. Sharp, *J. C. S. Perkin I*, 362 (1976).

The azocine **17** undergoes a similar cyclization to give the cyclobuta[*c*]pyridine **18**.¹⁷

2. 6π Systems

Relatively few examples of photochemically induced 6π -electrocyclizations of azahexa-1,3,5-trienes to azacyclohexa-1,3-dienes have been documented; the reverse process involving ring cleavage, however, is more common. The formation of azalumazin-7-ones **19** from triazahexatrienes **20** under oxidative conditions can be regarded as an example of such a process,¹⁸ but



¹⁷ R. M. Acheson, G. Paglietti, and P. A. Tasker, *J. C. S. Perkin I*, 2496 (1974).

¹⁸ F. Yoneda and M. Higuchi, *Chem. Pharm. Bull.* **25**, 2694 (1977).

in general alternative pathways are followed often leading to five-membered heterocycles. Ring cleavage is illustrated by the conversion of the 5,6-dihydropyridazine **21** to the two isomeric diazatrienes **22** and **23**,¹⁹ and analogous transformations have been postulated to account for more complex photoreactions such as, for example, the formation of cyclopent[*d*] [1,3]oxazines (**24**) from the corresponding *N*-acylcyclohexadienimines (**25**) via dienylketenimines (**26**).²⁰ Azahexatrienes, however, are not now believed to be intermediates in the photorearrangement of ethyl 2-cyano-1,2-dihydroquinoline-1-carboxylates.²¹

Reports of analogues of the stilbene-to-phenanthrene photocyclization are too numerous to list, particularly those in which a phenyl group has been replaced by a nitrogen heterocycle. Oxidation is effected by added iodine or by oxygen but in most cases evidence for the dihydro intermediate is slight. Thus, the novel 1,4,5,8-tetraazaphenanthrene system has been prepared in 90% yield by irradiation of 1,2-bis(pyrazyl)ethylene in benzene in the presence of oxygen.²² Photocyclizations in systems in which the carbon-carbon double bond is part of a heterocycle as in, for example, 4,5-diphenyloxazoles,²³ 2,3-diphenylindole,²⁴ and 1,3,4,5-tetraarylimidazolin-2-ones²⁵ have been effected in a similar fashion, and novel systems such as **27** can be synthesized in this way.²⁶ In conversions of the type *cis*-1-styrylimidazole (**28**) to imidazo[2,1-*a*]isoquinoline (**29**) in which a neutral dihydro intermediate is not possible, a dipolar species (**30**) has been proposed.²⁷

Oxidative photocyclization of benzylideneaniline appears to proceed efficiently only in the presence of strong acid. The phenanthridine **31**, however, has been prepared by irradiation of the imine **32**²⁸; few other examples of the photocyclization of arylimines have been reported.²⁹ Strong acid is also required for successful photocyclization of azobenzenes to benzo[*c*]cinnolines. Here, protonation is claimed to lower the reactive π , π^* excited state below the level of the unreactive *n*, π^* state. 2-Phenylazopyridine,

¹⁹ P. de Mayo and M. C. Usselman, *Can. J. Chem.* **51**, 1729 (1973).

²⁰ H. H. Eckhardt and H. Perst, *Tetrahedron Lett.*, 2125 (1979).

²¹ M. Ikeda, S. Matsugashita, and Y. Tamura, *Heterocycles* **9**, 281 (1978).

²² S. C. Shim and S. K. Lee, *Synthesis*, 116 (1980).

²³ V. N. R. Pillai and M. Ravindran, *Indian J. Chem., Sect. B* **15B**, 1043 (1977).

²⁴ C. A. Mudry and A. R. Frasca, *Tetrahedron* **30**, 2983 (1974).

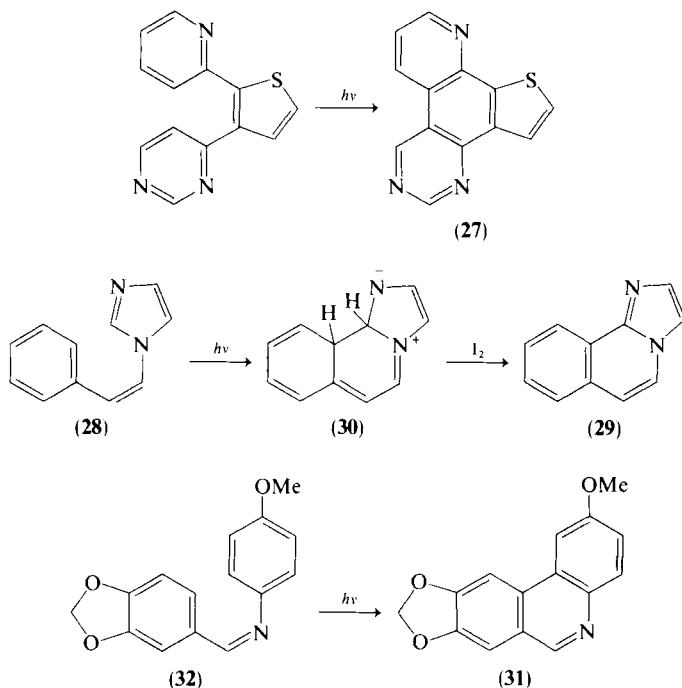
²⁵ O. Tsuge, K. Oe, and H. Inoue, *Heterocycles* **12**, 217 (1979).

²⁶ A. Mitschker, U. Brandl, and T. Kauffmann, *Tetrahedron Lett.*, 2343 (1974).

²⁷ G. Cooper and W. J. Irwin, *J. C. S. Perkin I*, 75 (1976).

²⁸ T. Onaka, Y. Kanda, and M. Natsume, *Tetrahedron Lett.*, 1179 (1974).

²⁹ B. Behjati and T. Bluhm, *J. Heterocycl. Chem.* **16**, 1639 (1979); J. S. Swenton, T. J. Ikeler, and G. L. Smyser, *J. Org. Chem.* **38**, 1157 (1973).



however, appears to undergo photocyclization to 4-pyrido[c]cinnoline in both acidic and neutral solution and the role of acid therefore remains uncertain.³⁰

The photocyclization of enamides has been the subject of detailed study and provides a valuable approach to the synthesis of alkaloids. A comprehensive review has been published.³¹ A variety of reaction types has been reported. The *N*-benzoylenamine **33**, for example, is converted on irradiation to the *trans*-lactam **34** by a process involving conrotatory photocyclization followed by a thermally allowed [1,5]-suprafacial hydrogen migration.³² The influence of substituents on this transformation has been studied.³³ The enacylamine **35** undergoes an analogous cyclization to give a mixture of *cis*- and *trans*-lactams **36**, the ratio of which is solvent

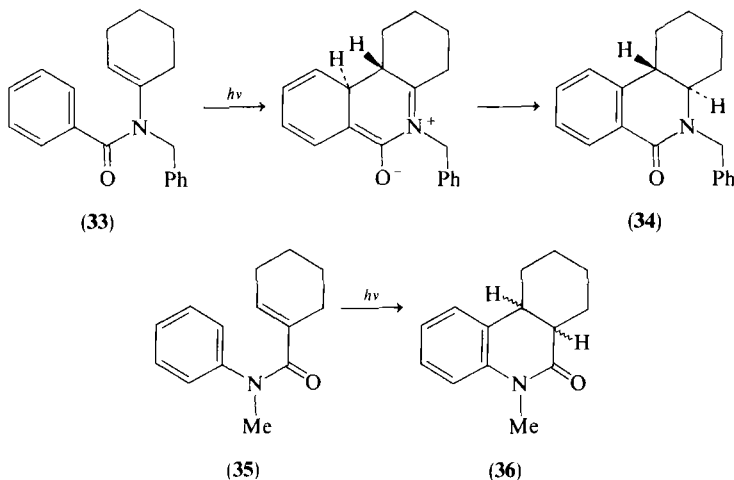
³⁰ V. N. R. Pillai and E. Purushothaman, *Curr. Sci.* **46**, 381 (1977).

³¹ G. R. Lenz, *Synthesis*, 489 (1978).

³² I. Ninomiya, T. Naito, T. Kiguchi, and T. Mori, *J. C. S. Perkin I*, 1696 (1973); I. Ninomiya, T. Naito, and T. Kiguchi, *ibid.*, 2257.

³³ I. Ninomiya, T. Kiguchi, O. Yamamoto, and T. Naito, *J. C. S. Perkin I*, 1723 (1979).

dependent.³⁴ Evidence for two different pathways leading respectively to *cis*- and *trans*-fused photoproducts has been reported in the nonoxidative cyclization of benzo[*b*]thiophen-2-carboxanilide and its *N*-methyl derivative.³⁵



The photocyclization of enamides has been widely employed in the construction of heterocyclic systems; the *N*-acryloyl-2-aminopyridines **37**, for example, are converted on irradiation to the lactams **38**.³⁶ Numerous benzylisoquinoline alkaloids have been prepared using this approach, and in particular, the syntheses of benzo[*c*]phenanthridine alkaloids have been reviewed.³⁷ Thus, irradiation of the [*Z*]-1-ethylidene-2-benzoyltetrahydroisoquinoline **39** affords the corresponding 8-oxoberberine **40**³⁸; competing photoisomerization to the *E*-isomer is observed but cyclization occurs only via the *Z*-isomer. Examples of syntheses of Amaryllidaceae and indole alkaloids have also been reported. In this way, the precursor **41** of (\pm)-lycoran has been obtained by oxidative cyclization of the enamide **42**.³⁹

The photochemically induced conversion of diarylamines into carbazoles is known to proceed via a similar cyclization pathway; a dipolar dihydro-

³⁴ I. Ninomiya, S. Yamauchi, T. Kiguchi, A. Shinohara, and T. Naito, *J. C. S. Perkin I*, 1747 (1974).

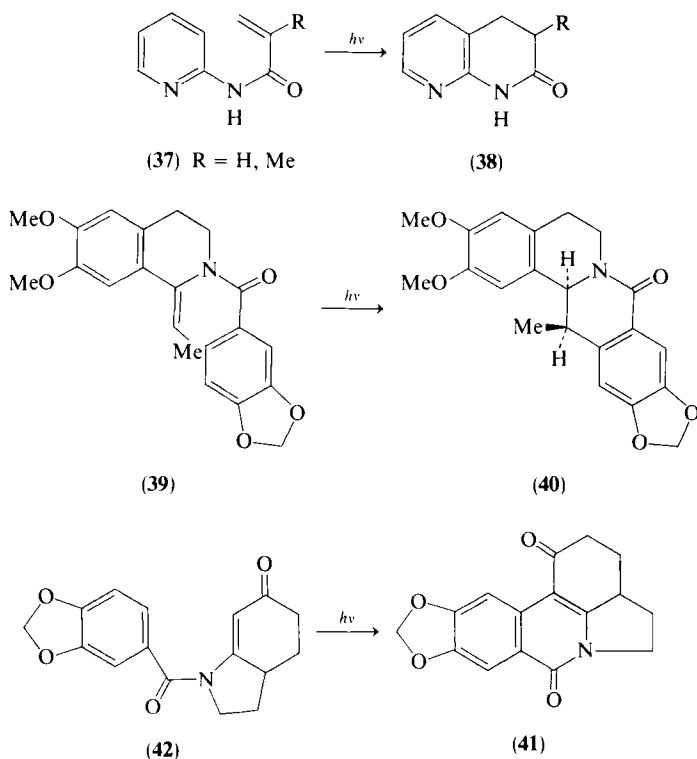
³⁵ Y. Kanaoka, K. Itoh, Y. Hatanaka, J. L. Flippen, I. L. Karle, and B. Witcop, *J. Org. Chem.* **40**, 3001 (1975).

³⁶ M. Ogata and H. Matsumoto, *Chem. Pharm. Bull.* **20**, 2264 (1972).

³⁷ I. Ninomiya, O. Yamamoto, T. Kiguchi, T. Naito, and H. Ishii, *Heterocycles* **6**, 1730 (1977).

³⁸ G. R. Lenz, *J. Org. Chem.* **41**, 2201 (1976).

³⁹ H. Iida, S. Aoyagi, Y. Yuasa, and C. Kibayashi, *Heterocycles* **6**, 1747 (1977).



carbazole intermediate has been detected spectroscopically.⁴⁰ Recent work has been concerned with the analogous cyclization of *N*-arylenamines. On irradiation, the enamine **43** is converted via a triplet excited state to a colored ground-state intermediate (**44**) which in turn affords the hexahydrocarbazole (**45**) by hydrogen migration.⁴¹ A 3-hydroxyindoline (**46**) is similarly obtained stereospecifically from 2-anilinoacetoacetate **47** by a process which presumably involves a conrotatory cyclization followed by a suprafacial [1,4] hydrogen migration.⁴² Included among the reported synthetic applications of this reaction is the formation in 90% yield of pyrazolo[3,4-*d*]pyrimidines (**48**) by oxidative cyclization of uracils (**49**).⁴³ Irradiation of diazoalkane **50** unexpectedly results in a 1,7-electrocyclic ring closure and the formation of the thienodiazepine **51**.⁴⁴

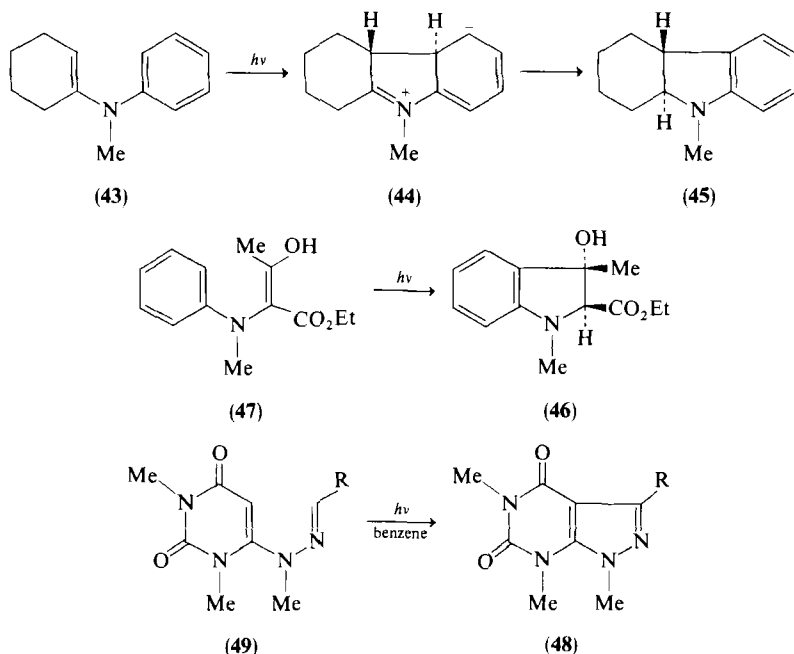
⁴⁰ E. W. Förster, K. H. Grellmann, and H. Linschitz, *J. Am. Chem. Soc.* **95**, 3108 (1973).

⁴¹ K. H. Grellmann, W. Kuehne, and T. Wolff, *Z. Phys. Chem. (Wiesbaden)* **101**, 295 (1976).

⁴² A. G. Schultz and W. K. Hagmann, *J. C. S. Chem. Commun.*, 726 (1976).

⁴³ F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Jpn.* **48**, 1484 (1975).

⁴⁴ D. P. Munro and J. T. Sharp, *J. Chem. Soc. Perkin, I*, 1718 (1980).



3. Nitrones and Heteroaromatic N-Oxides

One of the most rewarding and intensively investigated areas of research in heterocyclic chemistry has been the study of the photorearrangement of nitrones and heteroaromatic N-oxides. The subject was thoroughly reviewed in 1970.⁴⁵ A more recent review concerned with the photochemistry of aromatic N-oxides has been published.⁴⁶

Nitrones in general undergo a four-electron photocyclization to afford the corresponding oxaziridines. The process is stereospecific,⁴⁷ proceeds via the excited singlet state, and is in certain instances photochemically reversible.⁴⁸ Theoretical studies support this proposed pathway.⁴⁹ The nitrones **52**, on direct irradiation, afford the oxaziridines **53**, which on further irradiation are converted into the isomeric amides **54**.⁵⁰ In contrast, triplet

⁴⁵ G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.* **70**, 231 (1970).

⁴⁶ F. Bellamy and J. Streith, *Heterocycles* **4**, 1391 (1976).

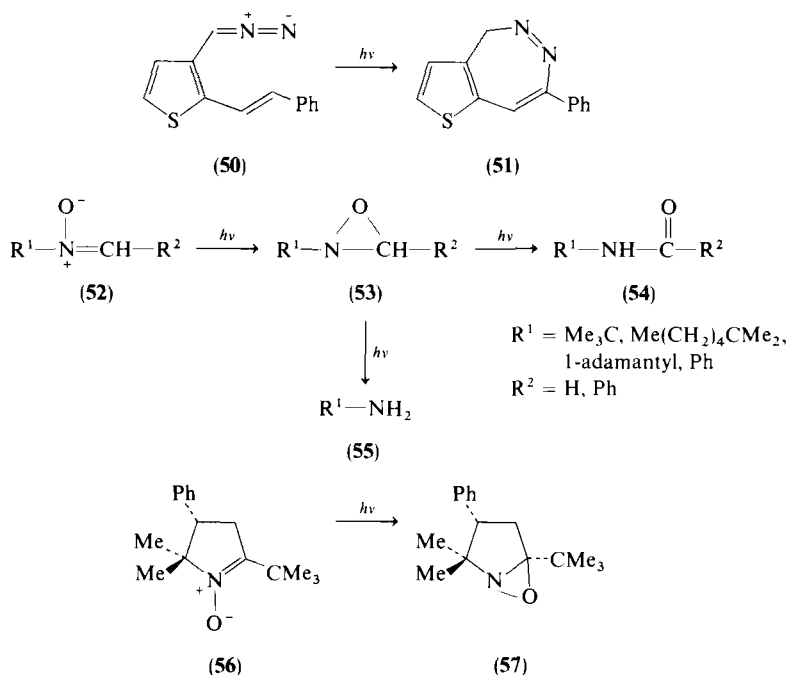
⁴⁷ D. R. Boyd, W. Jennings, and R. Spratt, *J. C. S. Chem. Commun.*, 745 (1970); H. Ono, J. S. Splitter, and M. Calvin, *Tetrahedron Lett.*, 4107 (1973).

⁴⁸ J. Bjorgo, D. R. Boyd, R. M. Campbell, and D. C. Neill, *J. C. S. Chem. Commun.*, 162 (1976).

⁴⁹ B. Bigot, D. Roux, A. Sevin, and A. Devaquet, *J. Am. Chem. Soc.* **101**, 2560 (1979).

⁵⁰ M. L. Druehlinger, R. W. Shelton, and S. R. Lammert, *J. Heterocycl. Chem.* **13**, 1001 (1976).

state decomposition of the oxaziridines proceeds via alkylnitrenes to give the corresponding amines **55**. Similar transformations have been reported in cyclic nitrenes. Thus, the pyrroline 1-oxide **56** is converted on irradiation to the oxaziridine **57**.⁵¹ Oxaziridines in turn frequently undergo further photochemical transformations. The 3*H*-indole 1-oxide **58**, for example, is converted on irradiation in cyclohexane via the oxaziridine (**59**) to the oxindole **60** and the 4-*H*-3,1-benzoxazine **61**.⁵² In methanol, however, the major product of irradiation is the isocyanate **62**. Oxaziridines have similarly been shown to be intermediates in the photochemically induced ring contraction of pyrroline 1-oxides to *N*-acylazetidines.⁵³



The use of chiral solvents in this photorearrangement has been shown to promote asymmetric synthesis of oxaziridines,⁵⁴ and application of the cyclization to highly substituted azoxy compounds provides a route to oxadiaziridines.⁵⁵

⁵¹ D. St. C. Black and K. G. Watson, *Aust. J. Chem.* **26**, 2505 (1973).

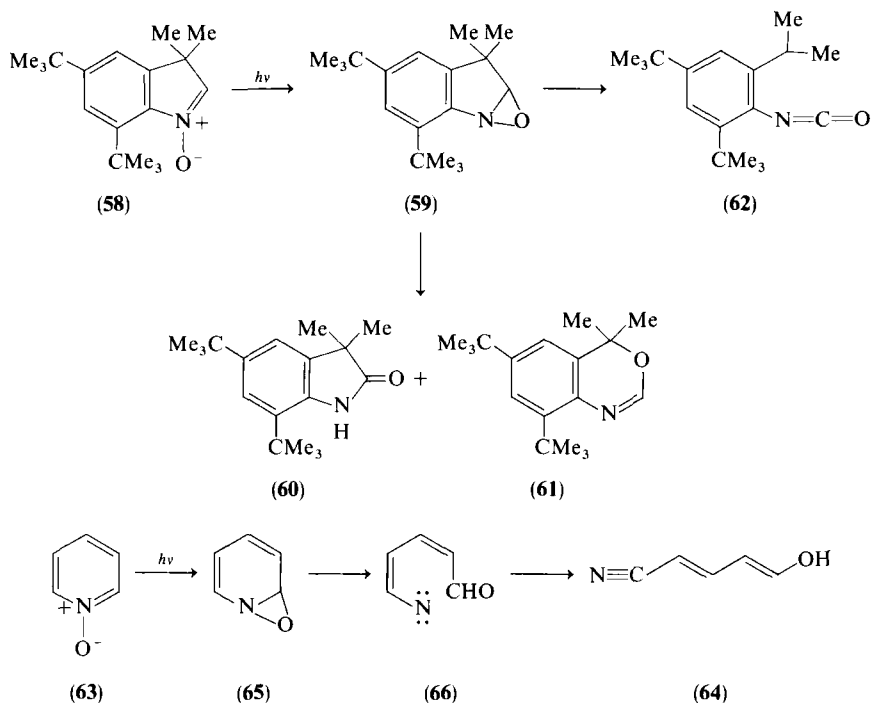
⁵² D. Dopp, *Chem. Ber.* **109**, 3849 (1976).

⁵³ D. St. C. Black and A. B. Boscacci, *Aust. J. Chem.* **30**, 1109 (1977).

⁵⁴ D. R. Boyd and D. C. Neill, *J. C. S. Chem. Commun.*, 51 (1977).

⁵⁵ F. D. Greene and S. S. Hecht, *J. Org. Chem.* **35**, 2482 (1970); W. R. Dolbier, K. Matsui, J. Michl, and D. V. Horak, *J. Am. Chem. Soc.* **99**, 3876 (1977).

The role of oxaziridines as intermediates in the rearrangement of hetero-aromatic N-oxides has not been fully established although in most cases the formation of photoproducts can best be rationalized in terms of such intermediates. Rearrangement appears to be singlet-derived and competes with triplet-derived deoxygenation.

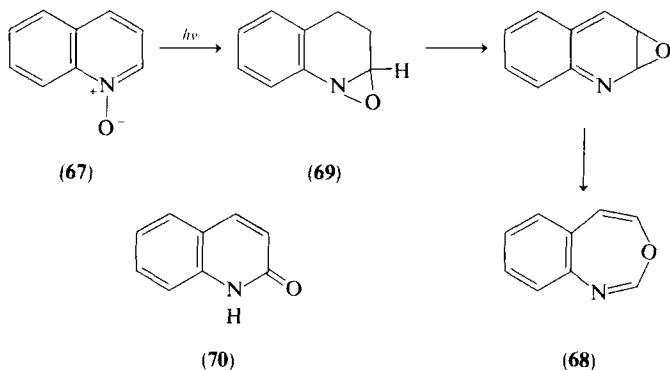


Irradiation of pyridine N-oxide (63) affords unstable products which undergo polymerization even at low concentrations.⁵⁶ In the presence of strong base, however, the anion of 5-hydroxypenta-2,4-dienenitrile (64) is obtained, and similarly with added secondary amine, derivatives of 5-aminopenta-2,4-dienenitrile have been isolated. These transformations are believed to proceed via the lowest excited singlet state and a series of excited state configurations, one of which corresponds to the oxaziridine 65, to give the ring-opened nitrene 66. 2,3,4,6-Tetraphenylpyridine N-oxide, on the other hand, undergoes photochemically induced ring expansion to give 1,3-oxazepines.⁵⁷ This process has been examined in greater detail in

⁵⁶ O. Buchardt, J. J. Christensen, P. E. Nielsen, R. R. Koganty, L. Finsen, C. Lohse, and J. Becher, *Acta Chem. Scand., Ser. B* **B34**, 31 (1980).

⁵⁷ O. Buchardt, C. L. Pedersen, and N. Harrit, *J. Org. Chem.* **37**, 3592 (1972).

quinoline *N*-oxide⁵⁸ and in 2-substituted quinoline *N*-oxides.⁵⁹ On irradiation in cyclohexane, quinoline *N*-oxide (**67**) is converted into the 1,3-benzoxazepine **68** by a pathway that is believed to involve the intermediate oxaziridine **69**. Irradiation in water gave exclusively quinol-(1*H*)2-one (**70**).



Other quinoline *N*-oxide derivatives have been examined. A 1,3-oxazepine is the major product of irradiation of 2-cyanoquinoline *N*-oxide whereas lactam formation predominates on irradiation of 4-methylquinoline *N*-oxide in aqueous ethanol.⁶⁰ Lactam formation has been shown to be influenced by an external magnetic field and on this basis it has been proposed that the first step in this transformation is the formation of an excited radical-ion pair.⁶¹ 1,3-Oxazepines undergo further reaction on prolonged irradiation. The synthesis of 4-substituted indoles, for example, has been accomplished in this way by irradiation of 5-substituted quinoline *N*-oxides.⁶²

Conflicting evidence for the intermediacy of oxaziridines in these and related photoreactions has been published. Evidence against the formation of oxaziridines in the photorearrangement of isoquinoline *N*-oxides has been described.⁶³ In contrast, the oxaziridine **71** has been detected on irradiation of 6-cyanophenanthridone 5-oxide (**72**) in an ethanol or 2-methyltetrahydrofuran matrix at 77 K leading eventually to 5-ethoxyphenanthridone (**73**) and 6-cyanophenanthridine (**74**), respectively.⁶⁴ 6-Cyano-3,1-dibenzoxazepine (**75**) was also obtained in both cases, presumably by an "oxygen walk" process involving oxaziridine **76**.

⁵⁸ A. Albini, G. F. Bettinetti, and G. Minoli, *Tetrahedron Lett.*, 3761 (1979).

⁵⁹ C. Kaneko and R. Kitamura, *Heterocycles* **6**, 111 (1977).

⁶⁰ N. Hata and T. Ogura, *Chem. Lett.*, 597 (1978).

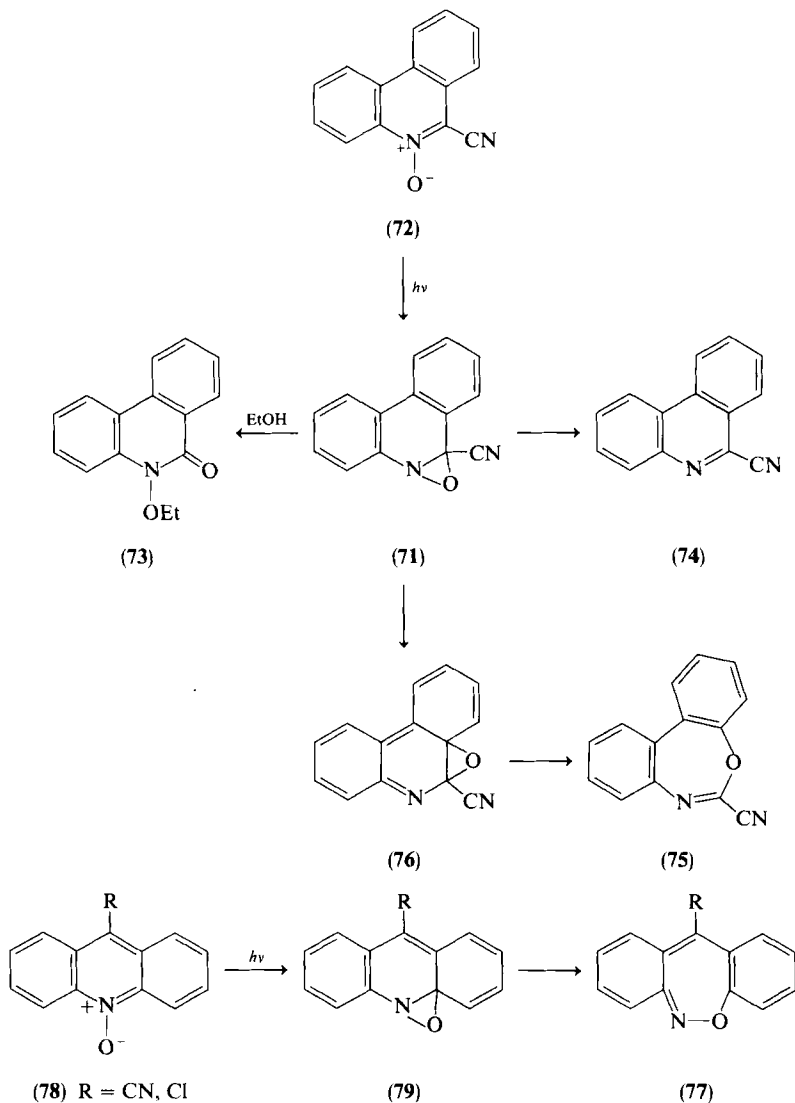
⁶¹ N. Hata, *Chem. Lett.*, 1359 (1978).

⁶² C. Kaneko, A. Yamamoto, and M. Hashiba, *Chem. Pharm. Bull.* **27**, 946 (1979).

⁶³ C. Lohse, *J. C. S. Perkin II*, 229 (1972).

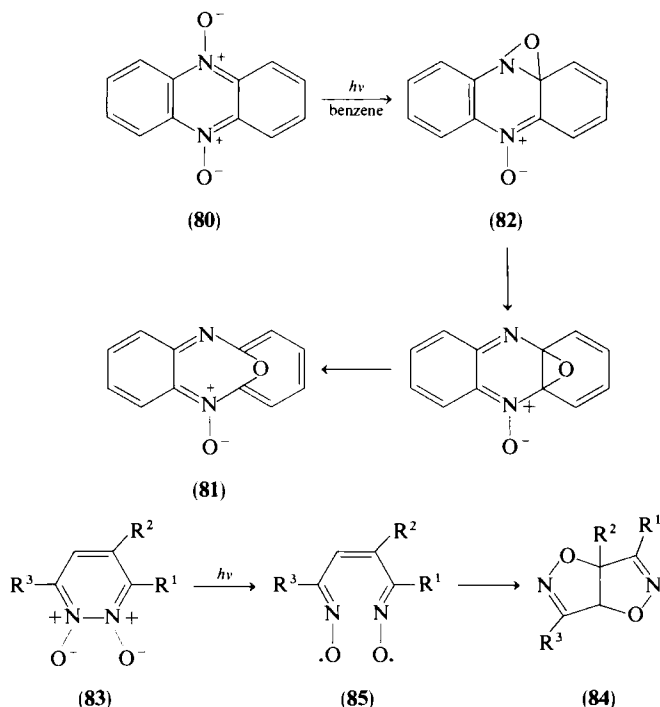
⁶⁴ K. Tokumura, H. Goto, H. Kashiwabara, C. Kaneko, and M. Itoh, *J. Am. Chem. Soc.* **102**, 5643 (1980).

Numerous examples of rearrangement in related systems have been reported. Oxazepines **77**, for example, have been isolated as the major products of irradiation in benzene of 9-cyano- and 9-chloroacridine 10-oxides (**78**) and are again believed to arise via oxaziridines **79**⁶⁵; products arising by further irradiation have also been described.⁶⁶ Diazine *N*-oxides



⁶⁵ S. Yamada and C. Kaneko, *Tetrahedron* **35**, 1273 (1979).

⁶⁶ S. Yamada, M. Ishikawa, and C. Kaneko, *Chem. Pharm. Bull.* **23**, 2818 (1975).



undergo similar transformation. Detailed studies of quinoxaline *N*-oxides,⁶⁷ pyrimidine *N*-oxides,⁶⁸ benzo[*a*]phenazine *N*-oxide,⁶⁹ and phenazine *N*-oxide⁷⁰ have been reported. The photorearrangement of phenazine *N,N*-dioxide (80) to the 1,6-oxido[10]annulene **81** can similarly be rationalized in terms of an intermediate oxaziridine (**82**).⁷¹ Different pathways appear to be preferred in pyridazine *N*-oxides; pyridazine 1,2-dioxides (**83**) are converted on irradiation in dichloromethane to isoxazolo[5,4-*d*]isoxazoles **84** by a process that is claimed to involve intermediate bisminoxyl radicals **85**.⁷² A transient diazoketone (**86**) has been detected spectroscopically in the photoreaction of 3,6-diphenylpyridazine *N*-oxide (**87**) to give the pyrazole **88** and the furan **89**⁷³; the proposed pathway is outlined in Scheme 1.

⁶⁷ A. Albini, R. Colombi and G. Minoli, *J. C. S. Perkin I*, 924 (1978); A. A. Jarrar, *J. Heterocycl. Chem.* **15**, 177 (1978); A. A. Jarrar and Z. A. Fataftah, *Tetrahedron* **33**, 2127 (1977).

⁶⁸ F. Roeterdink and H. C. van der Plas, *J. C. S. Perkin I*, 1202 (1976).

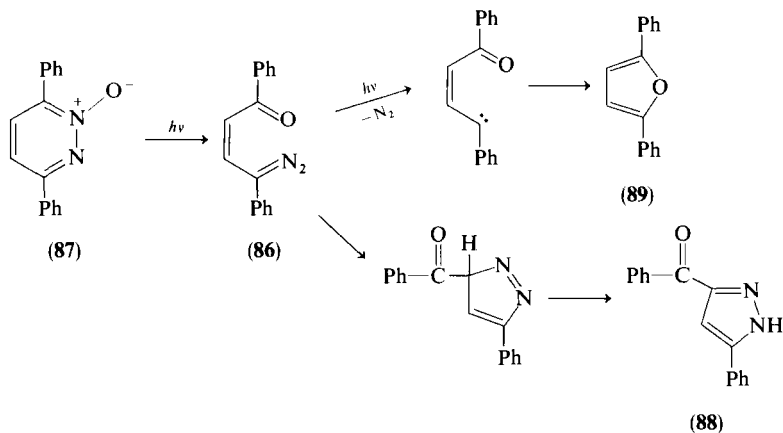
⁶⁹ C. Kaneko, S. Yamada, and M. Ishikawa, *Tetrahedron Lett.*, 2329 (1970).

⁷⁰ A. Albini, G. F. Bettinetti, and S. Pietra, *J. C. S. Perkin II*, 342 (1974).

⁷¹ H. Kawata, S. Nizuma, and H. Kokubun, *J. Photochem.* **9**, 463 (1978).

⁷² A. Ohsawa, H. Arai, H. Igeta, T. Akimoto, A. Tsuji, and Y. Iitaka, *Tetrahedron* **35**, 1267 (1979).

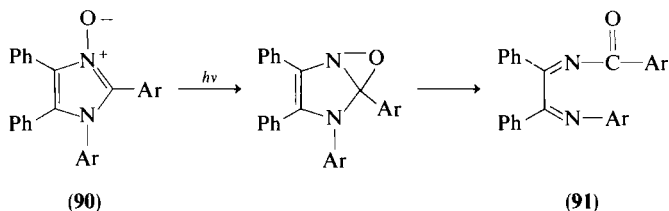
⁷³ K. B. Tomer, N. Harrit, I. Rosenthal, O. Buchardt, P. L. Kumler, and D. Creed, *J. Am. Chem. Soc.* **95**, 7402 (1973).



SCHEME 1

Evidence from nanosecond flash photolysis studies indicates that an oxaziridine precursor to the diazoketone is unlikely. Photoelimination of nitrogen is also observed in 4-methyl-1,2,3-benzotriazine 3-oxide and affords 3-methylantranil; a mechanism involving loss of nitrogen from an intermediate oxaziridine has been proposed.⁷⁴

Five-membered heteroaromatic N-oxides have been less systematically investigated although in most cases reaction via an intermediate oxaziridine appears to be involved. The imidazole 3-oxide **90**, for example, is converted on irradiation in polar or nonpolar media to the diimine **91**.⁷⁵



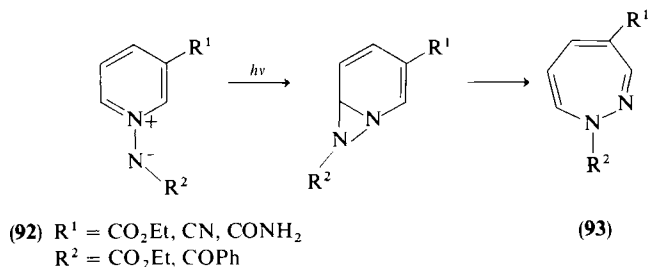
Iminopyridinium and iminoquinolinium ylids are known to undergo similar singlet derived ring expansion reactions.⁷⁶ These transformations are thought to proceed by way of diaziridine intermediates although attempts to trap or detect such transient intermediates by flash photolysis have proved unsuccessful. Evidence supporting the formation of diaziridines has, however,

⁷⁴ W. M. Horspool, J. R. Kershaw, A. W. Murray, and G. M. Stevenson, *J. Am. Chem. Soc.* **95**, 2390 (1973).

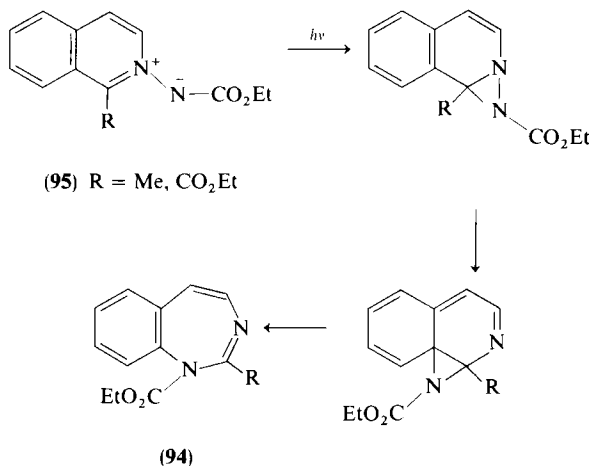
⁷⁵ G. J. Gainsford and A. D. Woolhouse, *J. C. S. Chem. Commun.*, 857 (1978).

⁷⁶ J. Streith, *Pure Appl. Chem.* **49**, 305 (1977); *Heterocycles* **6**, 2021 (1977).

been reported.⁷⁷ In contrast, triplet excitation leads to fragmentation and the formation of the parent heterocycle and a nitrene.



Regiospecific ring expansion has been observed on irradiation of the 3-substituted 1-iminopyridinium ylids **92** to give the 1H-1,2-diazepines **93**.⁷⁸ Various novel ring systems have been prepared in an analogous fashion. Thus, for example, the previously unknown 1H-1,3-benzodiazepines **94** were obtained by irradiation in dichloromethane of the isoquinoline *N*-imides **95**⁷⁹; a possible pathway is outlined in Scheme 2. The novel ring systems, 1H-1,3- and 3H-2,3-thieno[2,3-*d*]diazepines, have similarly been prepared by irradiation of 7-methylthieno[2,3-*c*]pyridine *N*-imides,⁸⁰ and



SCHEME 2

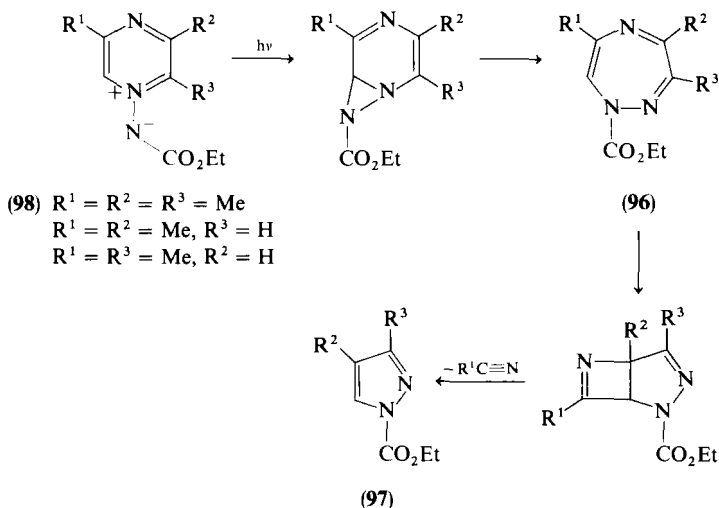
⁷⁷ H. Kwart, D. A. Benko, J. Streith, D. J. Harris, and J. L. Shuppiser, *J. Am. Chem. Soc.* **100**, 6501 (1978).

⁷⁸ H. Fritz, R. Gleiter, M. Nastasi, J. L. Schuppiser, and J. Streith, *Helv. Chim. Acta* **61**, 2887 (1978).

⁷⁹ T. Tsuchiya, M. Enkaku, J. Kurita, and H. Sawanishi, *J. C. S. Chem. Commun.*, 534 (1979).

⁸⁰ T. Tsuchiya, M. Enkaku, and H. Sawanishi, *Heterocycles* **12**, 1471 (1979).

1,2,5-triazepine intermediates **96** have been proposed to account for the formation of pyrazoles **97** and nitriles on irradiation of *N*-ethoxycarbonyl-iminopyrazinium ylids **98**.⁸¹



The formation of esters **99** by irradiation of 3-pyrazolidone azomethinimines **100** is the result of cyclization to diaziridines **101** followed by addition of methanol.⁸²

B. MISCELLANEOUS REACTIONS

1. Three- and Four-Membered Heterocycles

The photodecomposition of nitrogen, oxygen, and sulfur containing heterocycles has been reviewed.⁸³ The photochemistry of aziridine and its derivatives has been the subject of detailed investigations.⁸⁴ According to recent calculations, carbon–nitrogen bond cleavage is favored on irradiation in the gas phase whereas carbon–carbon cleavage competes in condensed protic media.⁸⁵ In the condensed phase, two primary photochemical processes have been observed, namely deamination and carbon–carbon

⁸¹ T. Tsuchiya, J. Kurita, and K. Ogawa, *J. C. S. Chem. Commun.*, 250 (1976).

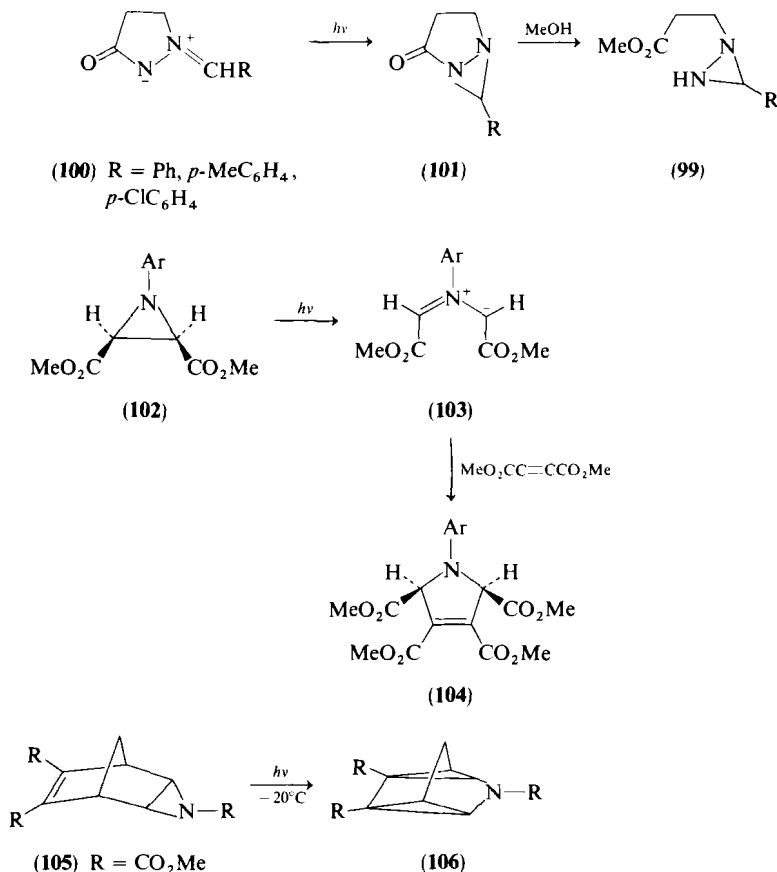
⁸² M. Schulz, G. West, U. Mueller, and D. Henke, *J. Prakt. Chem.* **318**, 946 (1976).

⁸³ S. Braslavsky and J. Hecklen, *Chem. Rev.* **77**, 473 (1977).

⁸⁴ N. R. Bertoniere and G. W. Griffin, *Org. Photochem.* **3**, 115 (1973).

⁸⁵ B. Bigot, A. Devaquet, and A. Sevin, *J. Org. Chem.* **45**, 97 (1980).

bond cleavage leading in the latter case to the formation of dipolar ylids. Such ring openings have been shown to proceed in a disrotatory fashion as predicted on the basis of orbital symmetry considerations; thus, the aziridine **102** is converted on irradiation to the ylid **103** which can readily be trapped as the dihydropyrrole **104** by reaction with dimethyl acetylenedicarboxylate.⁸⁶ The photoisomerization of *trans*-*N*-cyano-2,3-diphenylaziridine

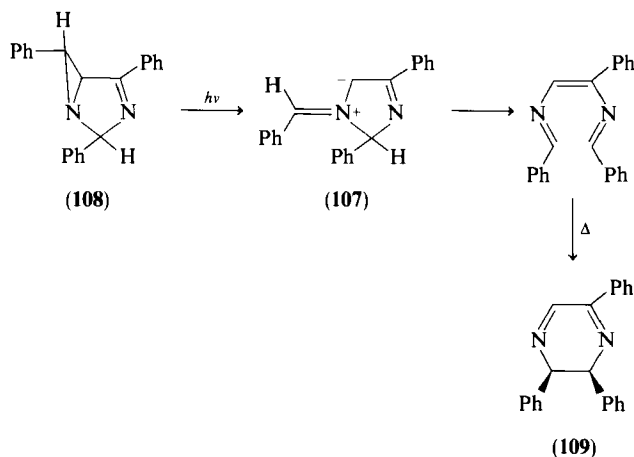


presumably involves an analogous intermediate,⁸⁷ and the rearrangement of aziridine **105** to the tetracycle **106** is at least formally the intramolecular equivalent of this process.⁸⁸ The intermediacy of an azomethine ylid (**107**) in the conversion of aziridine **108** into the *cis*-dihydropyrazine **109** has been

⁸⁶ R. Huisgen, W. Scheer, and H. Huber, *J. Am. Chem. Soc.* **89**, 1753 (1967).

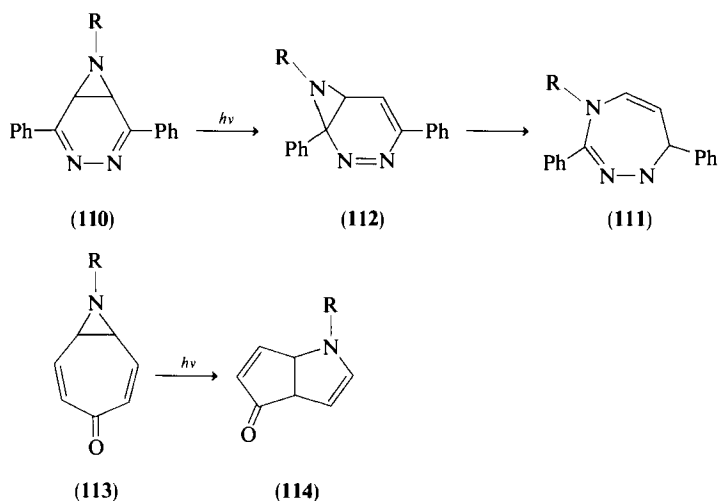
⁸⁷ A. G. Anastassiou and R. H. Hammer, *J. Am. Chem. Soc.* **94**, 303 (1973).

⁸⁸ M. Klaus and H. Prinzbach, *Angew. Chem., Int. Ed. Engl.* **10**, 273 (1971).



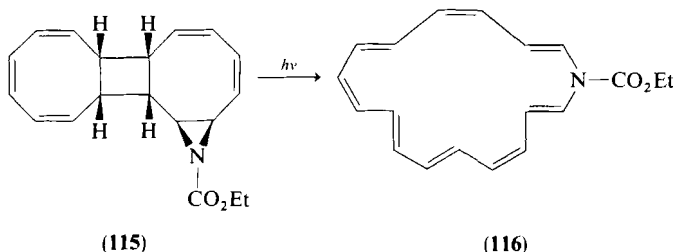
SCHEME 3

firmly established; the proposed pathway is outlined in Scheme 3.⁸⁹ Other ring-fused aziridines undergo novel photochemical reactions. Irradiation of the 3,4,7-triaza-2,4-norcaradienes **110**, for example, gives the previously unknown 4-substituted 1,2,4-triazepine system **111**; a “walk” rearrangement leading to the formation of the isomeric aziridine **112** is believed to be involved.⁹⁰ Details of the mechanisms responsible for the photorearrange-



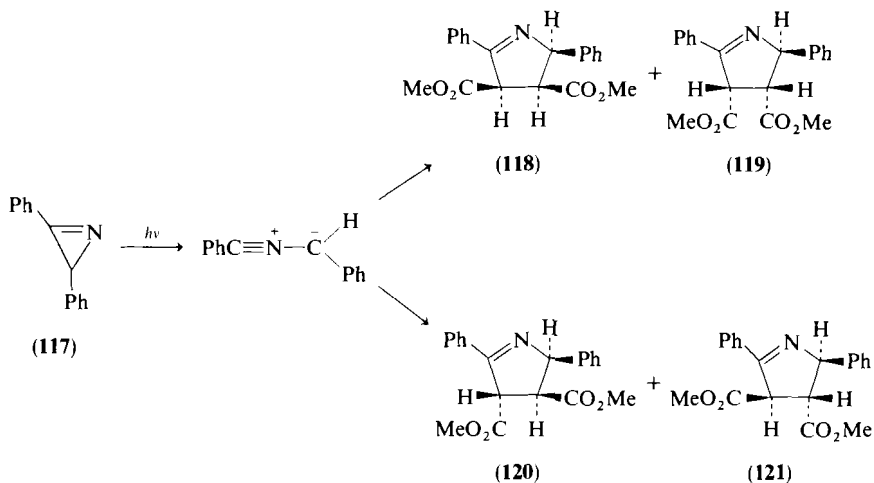
⁸⁹ A. Padwa and E. Glazer, *J. Am. Chem. Soc.* **94**, 7788 (1972).

⁹⁰ I. Saito, A. Yazaki, and T. Matsuura, *Tetrahedron Lett.*, 2459 (1976).



ments of aziridine **113** to dihydropyrrole **114**⁹¹ and of aziridine **115** to aza[17]annulene **116**⁹² are uncertain.

Independent work by Schmid⁹³ and by Padwa⁹⁴ on the photochemistry of 2*H*-azirines has shown that irradiation of such systems leads in the first instance to the formation of nitrile ylids (nitrilium betaines). Subsequent 1,3-addition to a variety of dipolarophiles affords five-membered heterocycles. These additions take place in a stereospecific and regioselective manner; thus, irradiation of the diphenyl-2*H*-azirine **117** in the presence of dimethyl maleate leads to the formation of the two isomeric 1-pyrrolines



118 and **119**, whereas irradiation in dimethyl fumarate affords the alternative isomers **120** and **121**.⁹⁵ Regiospecificity is observed in the corresponding additions to aldehydes, ketones, and esters, as shown, for example, by the

⁹¹ D. W. Jones, *J. C. S. Chem. Commun.*, 404 (1978).

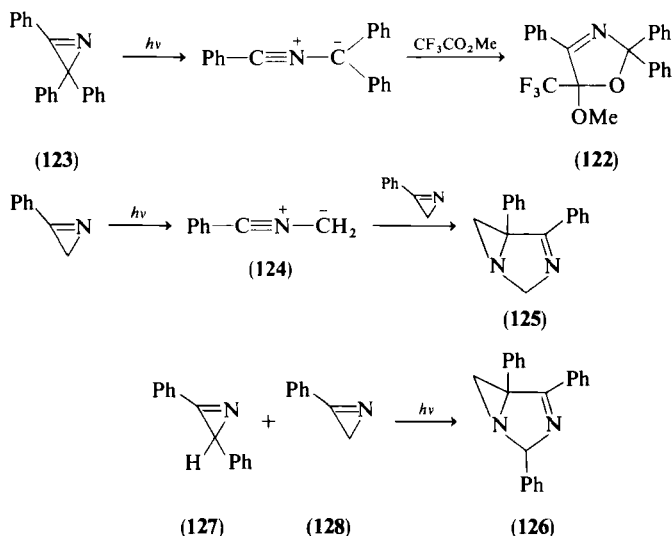
⁹² H. Röttele, G. Heil, and G. Schröder, *Chem. Ber.* **111**, 84 (1978).

⁹³ P. Gilgen, H. Heimgartner, H. Schmid, and H.-J. Hansen, *Heterocycles* **6**, 143 (1977).

⁹⁴ A. Padwa, *Angew. Chem., Int. Ed. Engl.* **15**, 123 (1976).

⁹⁵ A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, *J. Am. Chem. Soc.* **95**, 1945 (1973).

formation of oxazoline **122** from azirine **123** and methyl trifluoroacetate.⁹⁶ Analogous additions to nitriles,⁹⁷ thioesters,⁹⁸ isocyanates,⁹⁹ azodicarboxylates,¹⁰⁰ vinylphosphonium salts,¹⁰¹ and carbon dioxide¹⁰² have been reported. In the absence of a suitable dipolarophile, the photochemically generated nitrile ylid **124** undergoes 1,3-cycloaddition to ground state azirine to give the dimer **125**; a mixed dimer (**126**) arising from addition of



the ylid derived from azirine **127** to ground state azirine **128** has also been obtained.¹⁰³

The first example of a $[\pi 6 + \pi 4]$ cycloaddition of a nitrile ylid has recently been reported¹⁰⁴; irradiation of 3-phenyl-2,2-dimethyl-2*H*-azirine (**129**) in the presence of 6,6-dimethylfulvene (**130**) in cyclohexane gave the $[\pi 6 + \pi 4]$ adduct **131** together with the $[\pi 4 + \pi 2]$ adduct **132**.

⁹⁶ W. Sieber, P. Gilgen, S. Chaloupka, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta* **56**, 1679 (1973).

⁹⁷ B. Jackson, M. Maerky, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta* **55**, 919 (1972).

⁹⁸ A. Padwa, D. Dean, and J. Smolanoff, *Tetrahedron Lett.*, 4087 (1972).

⁹⁹ B. Jackson, N. Gakis, M. Maerky, H. J. Hansen, W. V. Philipborn, and H. Schmid, *Helv. Chim. Acta* **55**, 916 (1972).

¹⁰⁰ P. Gilgen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **57**, 1382 (1974).

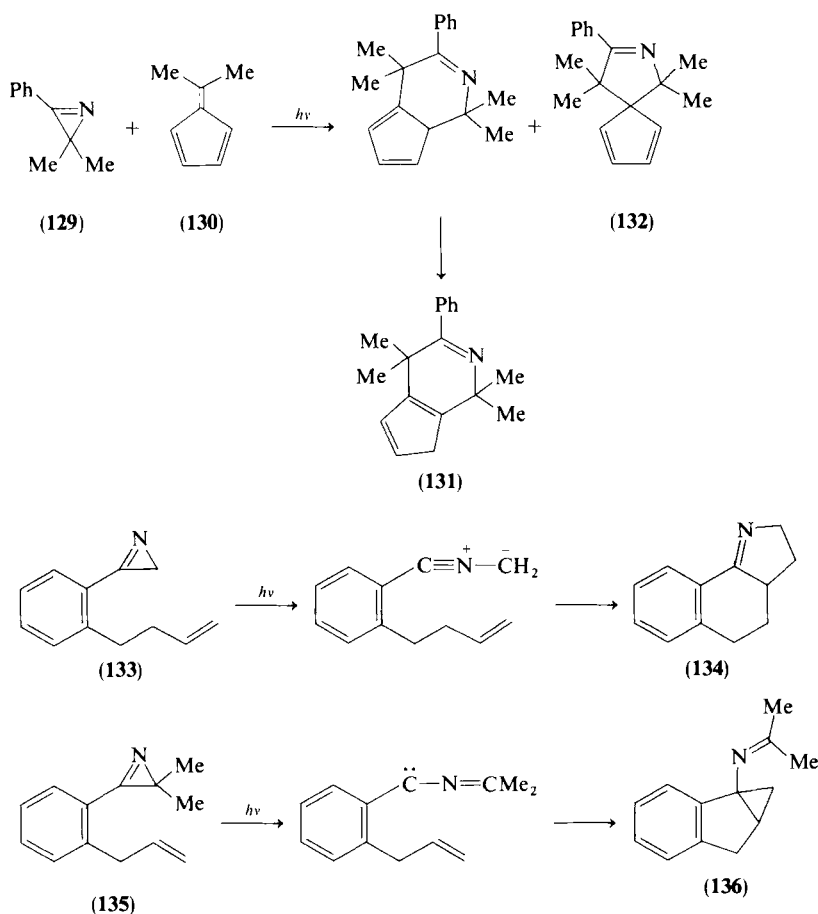
¹⁰¹ N. Gakis, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **57**, 1403 (1974).

¹⁰² N. Gakis, M. Märky, H. J. Hansen, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **59**, 2149 (1976).

¹⁰³ A. Padwa, J. Smolanoff, and S. I. Wetmore, *J. C. S. Chem. Commun.*, 409 (1972).

¹⁰⁴ A. Padwa and F. Nobs, *Tetrahedron Lett.*, 93 (1978).

Intramolecular nitrile ylid additions are increasingly attracting attention. In this way, irradiation of *o*-butenylphenyl-2*H*-azirine (133) gave the reduced benz[*g*]indole 134.¹⁰⁵ In contrast, irradiation of the *o*-allyl-2*H*-azirine 135 resulted in a nonconcerted 1,1-cycloaddition to give the cyclopropane 136. In the latter case, the normal "parallel plane" approach of linear nitrile ylid to the π -system is not possible, and an alternative 1,1-cycloaddition process via a species with bent geometry is preferred. The energy difference between such reactive intermediates is obviously small and it is not surprising therefore that reactions of this type are readily influenced by substituents.¹⁰⁶ Intramolecular ylid addition to a carbonyl group, as illustrated

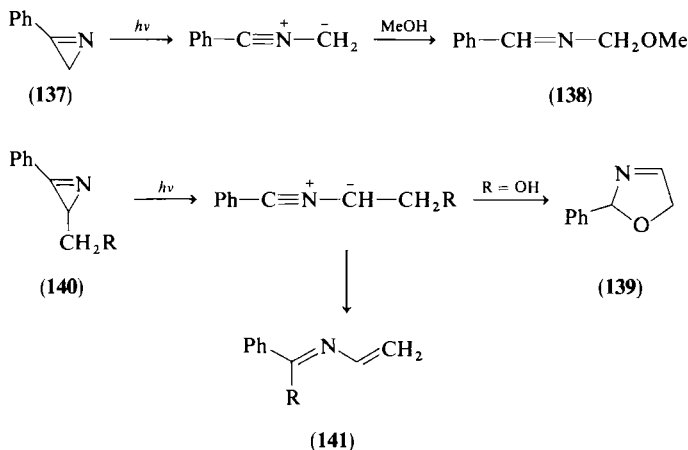


¹⁰⁵ A. Padwa and A. Ku, *J. Am. Chem. Soc.* **100**, 2181 (1978).

¹⁰⁶ A. Padwa, P. H. J. Carlsen, and A. Ku, *J. Am. Chem. Soc.* **100**, 3494 (1978).

by the conversion of 2-formyl-3-phenyl-2*H*-azirine into 2-phenyloxazole, has also been described.¹⁰⁷

Nitrile ylids generated in this way can be trapped with methanol¹⁰⁸ Thus, on irradiation in methanol, the azirine **137** was converted to the methoxy-imine (**138**). The intramolecular equivalent reaction leading to the oxazoline **139** has also been observed on irradiation of the 2*H*-azirine (**140**; R = OH),



and occurs in virtually quantitative yield. Surprisingly, the related 2*H*-azirines (**140**; R = Cl, Br, or OAc) undergo a novel photorearrangement to give 1-substituted 1-phenyl-2-azabutadienes **141**.¹⁰⁹

Aziridinones on excitation undergo loss of carbon monoxide with the formation of the corresponding imines.¹¹⁰ The role of oxaziridines in the photorearrangement of nitrones has already been discussed. Oxaziridines have also been proposed as intermediates in the photorearrangement of oximes to amides and lactams. Cycloalkanone oximes containing 4 to 15 carbon atoms are known to give high yields of the corresponding lactams on irradiation in methanol¹¹¹ Indeed, 2,2,6,6-tetramethylcyclohexanone oxime is converted in this way into a caprolactam in 60% yield, a transformation that is not realized under normal Beckmann rearrangement conditions. Similarly, α -hydroxylactams have been prepared by photorearrangement of cyclic α -hydroxyketoximes, a conversion which is also

¹⁰⁷ A. Padwa, J. Smolanoff, and A. Tremper, *J. Am. Chem. Soc.* **97**, 4682 (1975).

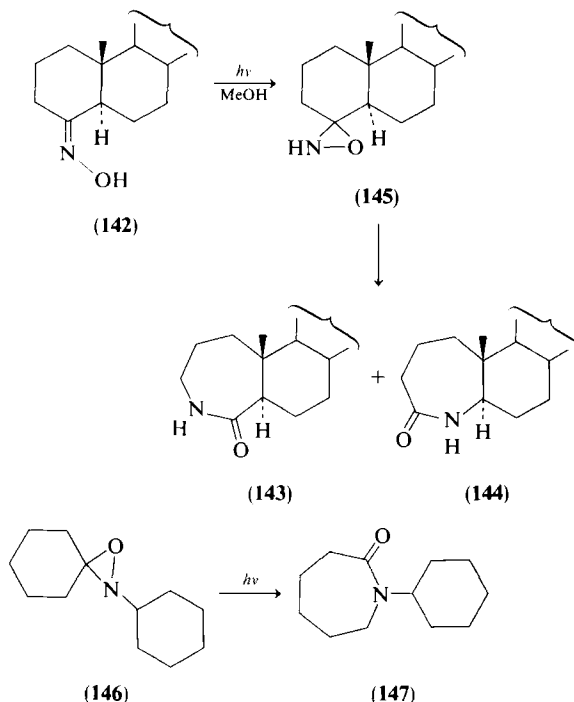
¹⁰⁸ A. Padwa, J. K. Rasmussen, and A. Tremper, *J. Am. Chem. Soc.* **98**, 2605 (1976).

¹⁰⁹ A. Padwa, P. H. J. Carlsen, and A. Tremper, *J. Am. Chem. Soc.* **100**, 4481 (1978).

¹¹⁰ E. R. Talaty, A. E. Dupuy, and T. H. Golson, *J. C. S. Chem. Commun.*, 49 (1969); J. C. Sheehan and M. M. Nafissi, *J. Am. Chem. Soc.* **91**, 1176 (1969).

¹¹¹ L. S. Ng Lim and G. Just, *Can. J. Chem.* **49**, 2891 (1971).

not possible under Beckmann reaction conditions.¹¹² The stereochemistry of the migrating group is retained in the Beckmann photorearrangement as shown, for example, in the conversion of 5 α -cholestan-4-one oxime **142** to the isomeric lactams **143** and **144**; evidence for a singlet-derived intermediate oxaziridine **145** has been published.¹¹³ The photorearrangement of individual spirooxaziridines has been examined.¹¹⁴ The oxaziridine



146, for example, readily affords *N*-cyclohexylcaprolactam **147** on irradiation.¹¹⁵

The photoreactions of four-membered nitrogen containing heterocycles have been less well investigated and meaningful results are confined to certain azetidines and azetidinones. The photochemically induced rearrangement of azetidines **148** to 1,4-diazepines **149** has been rationalized in terms of a process equivalent to a di- π -methane rearrangement¹¹⁶; a more

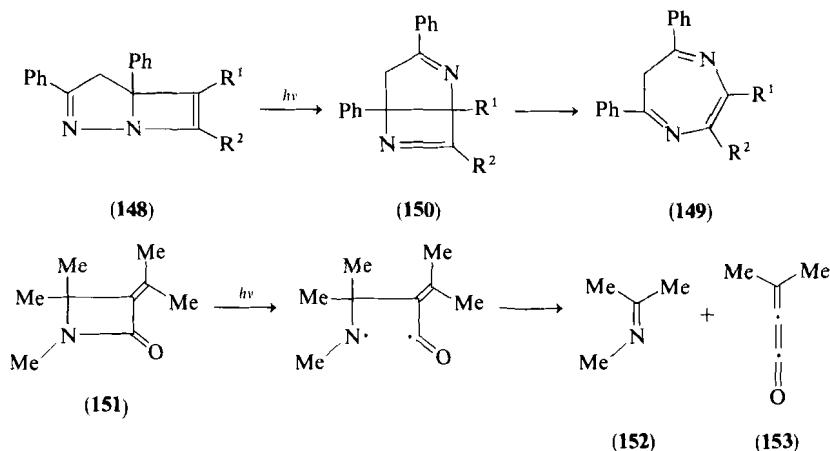
¹¹² H. Suginome and C.-M. Shea, *Synthesis*, **229** (1980).

¹¹³ H. Suginome and F. Yagihashi, *J. C. S. Perkin I*, 2488 (1977).

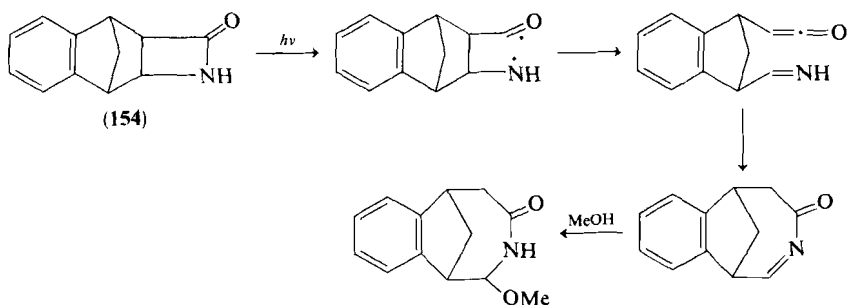
¹¹⁴ E. Oliveros, M. Rivière, and A. Lattes, *Nouv. J. Chim.* **3**, 739 (1979); Y. Kobayashi, *Bull. Chem. Soc. Jpn.* **46**, 3467 (1973).

¹¹⁵ S. T. Reid and E. J. Wilcox, *Tetrahedron Lett.*, 1759 (1972).

¹¹⁶ G. Reissenweber and J. Sauer, *Tetrahedron Lett.*, 4389 (1977).



persuasive explanation involving nitrogen–nitrogen bond homolysis and a 1,3-shift to give azetines **150** followed by electrocyclic ring opening can be advanced. Electrocyclic ring cleavage has been reported in an azetidino-[3,2-*b*]pyridine.¹¹⁷ Initial carbon–nitrogen bond homolysis is responsible for the conversion of the isopropylideneazetidin-2-one **151** to the imine **152** and isopropylideneketene **153**.¹¹⁸ An analogous transformation has been observed on irradiation in methanol of the fused bicyclo[2.2.1]heptene **154**¹¹⁹; bond cleavage is followed by intramolecular addition of the resulting imine to the ketene and by solvent addition as shown in Scheme 4. Photochemically induced ring expansion of azetidine-2,4-diones to isoxazolidones has also been reported.¹²⁰



SCHEME 4

¹¹⁷ J. W. Lawn, M. H. Akhtar, and W. M. Dadson, *J. Org. Chem.* **40**, 3363 (1975).

¹¹⁸ P. H. Mazzocchi, M. W. Bowen, and J. Kachinsky, *J. C. S. Chem. Commun.*, 53 (1977).

¹¹⁹ P. H. Mazzocchi, T. Halchak, and H. J. Tamburin, *J. Org. Chem.* **41**, 2808 (1976).

¹²⁰ J. A. Schutyser and F. C. De Schryver, *Chem. Ind. (London)*, 465 (1972).

2. Five- and Six-Membered Heterocycles

A wide variety of photochemical transformations have been reported in five- and six-membered heterocycles and their derivatives. One of the most thoroughly investigated areas is that concerned with the photorearrangement of heteroaromatic systems. Ketoazirines have long been postulated as intermediates in the photorearrangement of isoxazoles to oxazoles. These species have now been fully characterized and, in a number of cases, isolated. Pyrex-filtered irradiation of the isoxazolophane **155** in acetone, for example, gave the azirine **156**.¹²¹ Further photorearrangement of this azirine appears to be wavelength dependent; irradiation ($\lambda = 254$ nm) gave the corresponding oxazolophane **157** whereas irradiation ($\lambda > 300$ nm) gave a species tentatively assigned the ketoketenimine structure **158**. An isocyanide (**159**), however, has been established as an additional intermediate in the photorearrangement of isoxazole **160** to oxazole **161** at -77°C .¹²² The isocyanide is believed to arise via the azirine **162**, as suggested by spectroscopic evidence. Analogous ring transposition reactions have been reported in 3-hydroxyisoxazoles,¹²³ but more complicated photo-reactions have been observed in isoxazol-5-ylhydrazines.¹²⁴ The photorearrangement of benzisoxazoles to benzoxazoles has also been shown to proceed via azirines. The spiroazirines **163**, for example, have been detected spectroscopically as intermediates in the conversion of benzisoxazoles **164** to benzoxazoles **165**.¹²⁵ Strong evidence for the intermediacy of isocyanides in these transformations has been reported.¹²⁶ Many similar photorearrangements such as the formation of oxazolo[5,4-*b*]pyridines from isoxazolo[5,4-*b*]pyridines¹²⁷ have been described in the literature.

The reverse process has also been examined. 2-Phenyloxazole is converted in a similar fashion to 3-phenyl-2*H*-azirine-2-carbaldehyde on irradiation in benzene or cyclohexane.¹²⁸ Further rearrangement to the corresponding isoxazole can be effected thermally but not photochemically. A competing pathway leading to the formation of 4-phenyloxazole has also been observed and is thought to involve a bicyclic intermediate arising by 2,5-bonding.

¹²¹ S. Albanesi and A. Marchesini, *Tetrahedron Lett.*, 1875 (1979).

¹²² J. P. Ferris and R. W. Trimmer, *J. Org. Chem.* **41**, 13 (1976).

¹²³ M. Nakagawa, T. Nakamura, and K. Tomita, *Agric. Biol. Chem.* **38**, 2205 (1974).

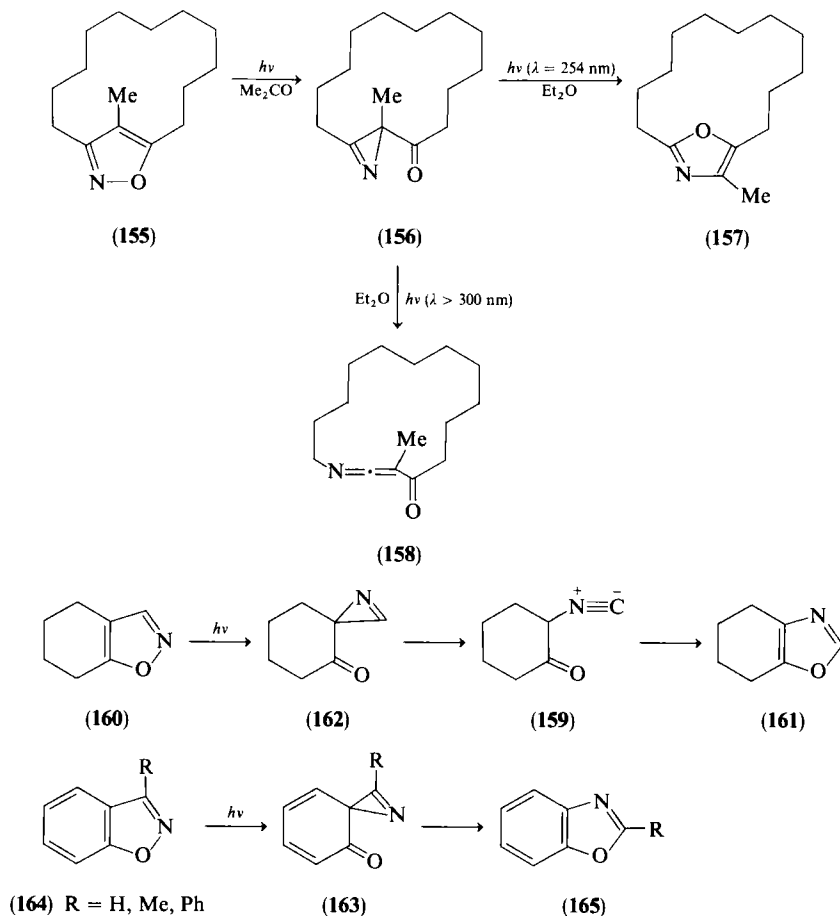
¹²⁴ G. Adembri, A. Camparini, D. Donati, F. Ponticelli, and P. Tedeschi, *Tetrahedron Lett.*, 4439 (1978).

¹²⁵ K. H. Grellmann and E. Tauer, *J. Photochem.* **6**, 365 (1977).

¹²⁶ J. P. Ferris and F. R. Antonucci, *J. Am. Chem. Soc.* **96**, 2014 (1974); K. H. Grellmann and E. Tauer, *Tetrahedron Lett.*, 375 (1974).

¹²⁷ C. Skötsch and E. Breitmaier, *Chem. Ber.* **112**, 3282 (1979).

¹²⁸ M. Maeda and M. Kojima, *J. C. S. Perkin I*, 239 (1977).

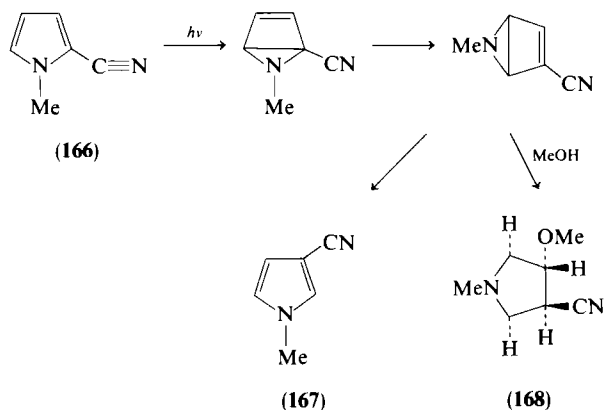


The principal products of irradiation of 2-cyano-1-methylpyrrole (**166**) in methanol, however, are the corresponding 3-cyanopyrrole **167** and the methanol adduct **168**.¹²⁹ These products appear to arise by a 2,5-bonding process followed by a thermal "walk" rearrangement as shown in Scheme 5.

Ring transposition reactions have also been described in diazoles. 1,4-Dimethylimidazole is converted on irradiation in *tert*-butyl alcohol to the 1,2-dimethyl isomer in 40% yield.¹³⁰ Similarly, the isomeric trimethylimidazoles **169** and **170** have been obtained by irradiation of 1,3,5-trimethylpyrazole (**171**) in ethanol. The reported conversion of acylpyrazoles to 1,2-bis(1-arylimidazol-4-yl)ethane-1,2-diols must also involve a photo-

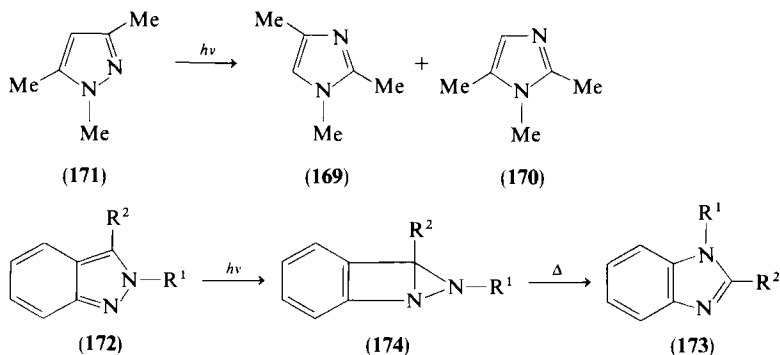
¹²⁹ J. A. Barltrop, A. C. Day, and P. W. Ward, *J. C. S. Chem. Commun.*, 131 (1978).

¹³⁰ P. Beak and W. Messer, *Tetrahedron* **25**, 3287 (1969).



SCHEME 5

chemically induced ring transposition in addition to photoreduction.¹³¹ An intermediate, stable at -60°C , in the photoisomerization of 2-alkylindazoles (**172**) to the corresponding 1-alkylbenzimidazoles (**173**) is thought to have the tricyclic structure **174**.¹³² The effect of acid on these photo-reactions has been studied.¹³³ Benzofurazan (**175**) fragments in a different manner on irradiation in methanol to give the carbamate **176**¹³⁴; intermediates **177** and **178** have been detected spectroscopically and the reaction is believed to proceed via the acylnitrene **179** which can be trapped by benzene as the azepine **180**. Anthranils, on the other hand, on irradiation in methanol undergo ring expansion to azepines.¹³⁵



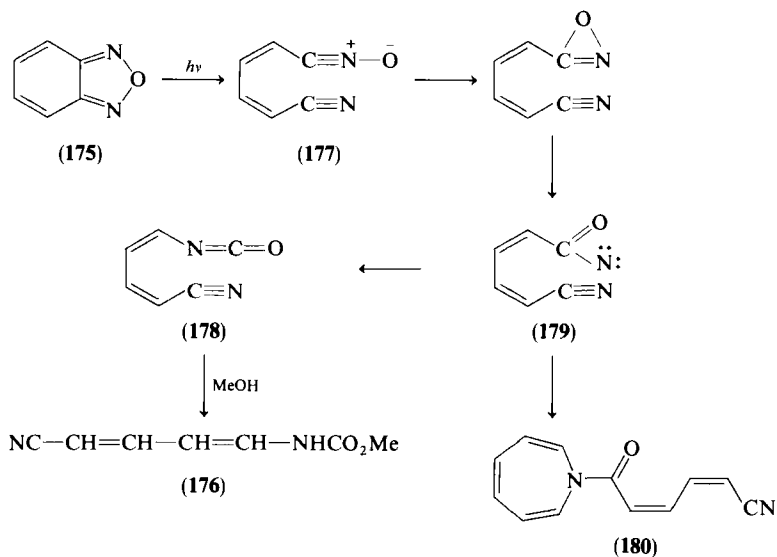
¹³¹ T. Nishiwaki, F. Fujiyama, and E. Minamisono, *J. C. S. Perkin I*, 1871 (1974).

¹³² W. Heinzelmann, M. Märky, and P. Gilgen, *Helv. Chim. Acta* **59**, 1512 (1976).

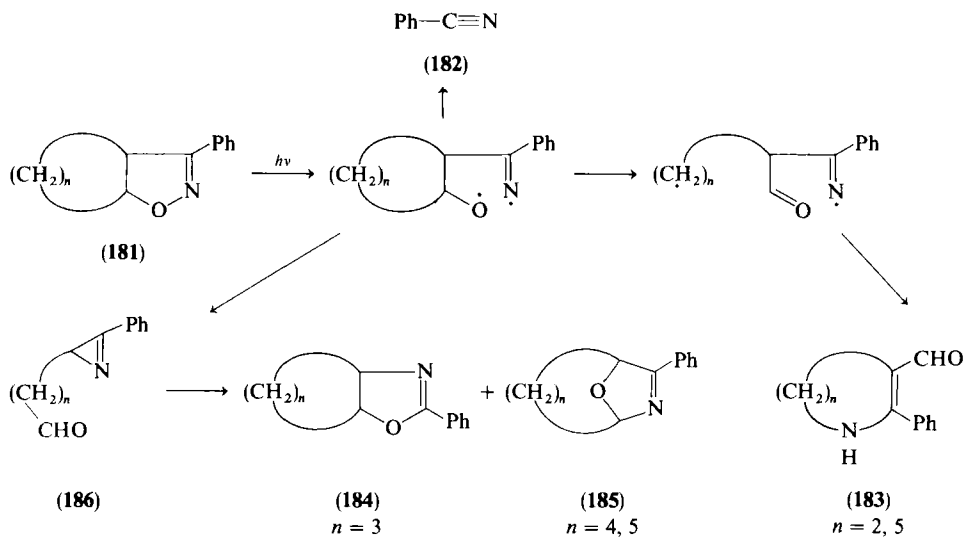
¹³³ W. Heinzelmann, M. Märky, and P. Gilgen, *Helv. Chim. Acta* **59**, 2362 (1976).

¹³⁴ W. Heinzelmann and P. Gilgen, *Helv. Chim. Acta* **59**, 2727 (1976).

¹³⁵ M. Ogata, H. Matsumoto, and H. Kano, *Tetrahedron* **25**, 5205 (1969).



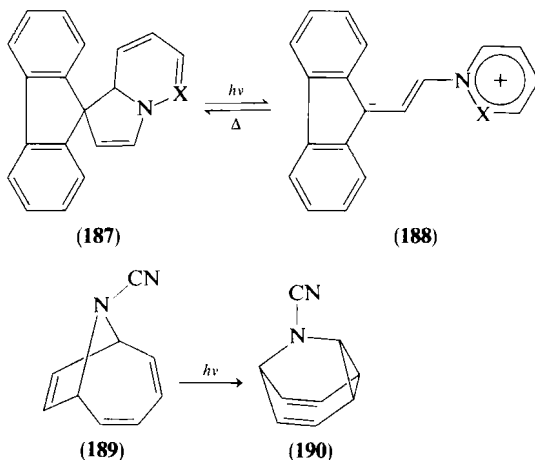
Analogous intermediates seem to be involved in at least some of the reported photoreactions of related dihydroheteroaromatic systems. On irradiation in benzene, the isoxazolines **181** are converted to benzonitrile (**182**) and the aldehydes **183** via fragmentation pathways (see Scheme 6)



SCHEME 6

and into the oxazolines **184** and **185** via the azirines **186**.¹³⁶ In one case, that of $n = 2$, the intermediate azirine **186** has been isolated. The photoisomerization of iminoisoxazolines to the corresponding imidazolones is also believed to arise by initial nitrogen–oxygen bond homolysis.¹³⁷

A wide variety of other photoreactions has been reported in five-membered heterocycles. 1,8a-Dihydroindolizines (**187**), for example, undergo ring cleavage to form thermally unstable photoproducts (**188**),¹³⁸ whereas sensitized irradiation of the azatriene **189** provides a route to 9-azabarbaralane (**190**).¹³⁹ Examples of photochemically induced ring opening in dihydrodiazoles have also been described.¹⁴⁰ Such a transformation has been observed in the 1,5-diazabicyclo[3.3.0]octa-2,6-dienes **191** and leads, presumably via the intermediates **192**, to the tetraenes **193**.¹⁴¹ Irradiation of 1-pyrazolines is normally accompanied by the elimination of nitrogen. Alternative pathways have been observed in a few cases; 7,8-diazatetracyclo[3.3.0^{2,4}0^{3,6}]oct-7-ene, for example, is converted on direct and acetophenone-sensitized irradiation into 1,2-diazocine,¹⁴² and extensive conjugation of the oxiran with the azo function in the 1-pyrazoline **194** is



¹³⁶ O. Seshimoto, T. Kumagai, K. Shimizu, and T. Mukai, *Chem. Lett.*, 1195 (1977).

¹³⁷ H. G. Aurich and G. Blinne, *Chem. Ber.* **107**, 13 (1974).

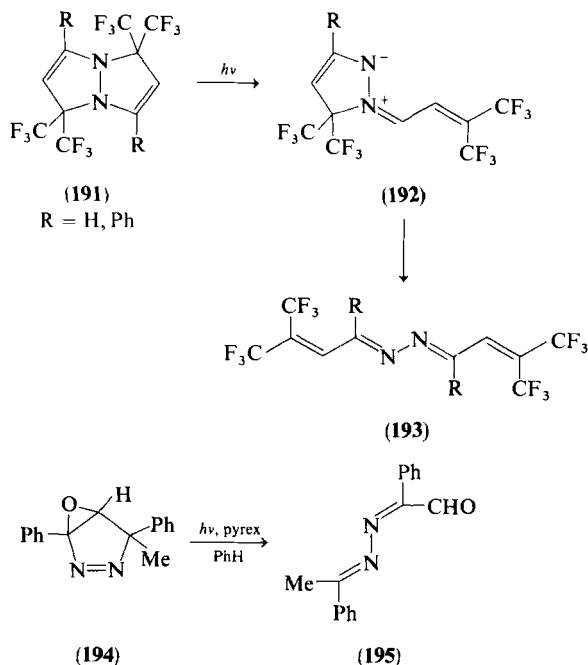
¹³⁸ G. Hauck and H. Dürr, *Angew. Chem., Int. Ed. Engl.* **18**, 945 (1979).

¹³⁹ A. G. Anastassiou, A. E. Winston, and E. Reichmanis, *J. C. S. Chem. Commun.*, 779 (1973).

¹⁴⁰ T. Matsuura and Y. Ito, *Bull. Chem. Soc. Jpn.* **48**, 3369 (1975); L. Schrader, *Tetrahedron Lett.*, 2977 (1971).

¹⁴¹ K. Burger, C. Zettl, F. Hein, and H. Schickaneder, *Chem. Ber.* **112**, 2620 (1979).

¹⁴² B. M. Trost, P. H. Scudder, R. M. Cory, N. J. Turro, V. Ramamurthy, and T. J. Katz, *J. Org. Chem.* **44**, 1264 (1979).



claimed to be responsible for the preferred photorearrangement to the aldehyde **195**.¹⁴³

Numerous examples of ring cleavage and related transformations have been reported in carbonyl containing heterocycles such as pyrrolidinones,¹⁴⁴ pyrrolidinediones,¹⁴⁵ pyrazolones,¹⁴⁶ and oxazolones.¹⁴⁷ Of particular note is the conversion of the ketoimino ether **196** into the bicyclo[*n*.1.0]-alkanes **197** in which a Norrish Type I process is believed to be involved¹⁴⁸ and the photochemically induced ring contraction of 2-acylpyrazolidin-3-one (**198**) to *N*-acylaminoazetidin-2-one (**199**).¹⁴⁹ 2-Nitropyrrole (**200**) undergoes photorearrangement to give the oxime **201** by a pathway thought to involve the unsaturated nitrite **202**.¹⁵⁰ In contrast, a bridging pathway has been

¹⁴³ L. E. Freidrich, N. L. de Vera, and Y. P. Lam, *J. Org. Chem.* **43**, 34 (1978).

¹⁴⁴ D. Döpp and H. Weiler, *Chem. Ber.* **112**, 3950 (1979).

¹⁴⁵ Y. Kanaoka, H. Okajima, and Y. Hatanaka, *J. Org. Chem.* **44**, 1749 (1979); K. Maruyama, T. Ishitoku, and Y. Kubo, *J. Am. Chem. Soc.* **101**, 3670 (1979).

¹⁴⁶ J. Reisch and W. F. Ossenkop, *Chem. Ber.* **106**, 2070 (1973); J. Reisch and A. Fitzek, *Arch. Pharm. (Weinheim, Ger.)* **307**, 211 (1974).

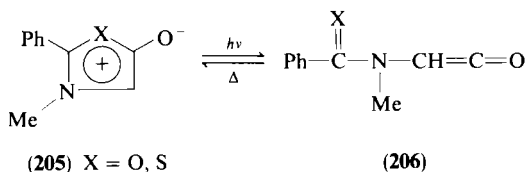
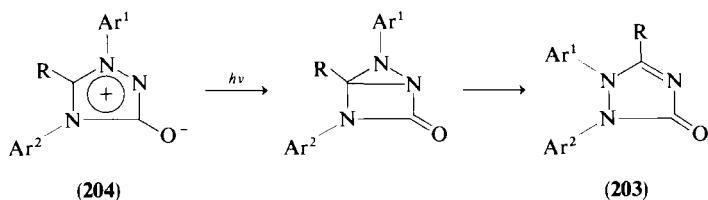
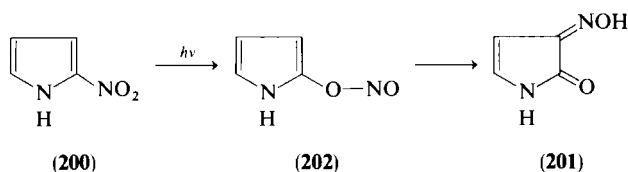
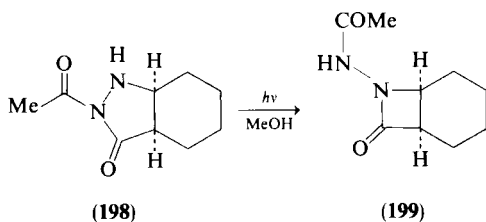
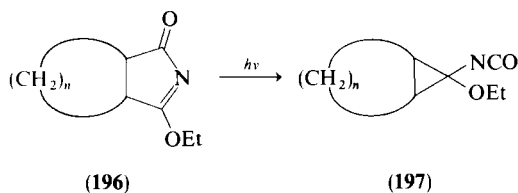
¹⁴⁷ J. H. Jones and M. J. Witty, *J. C. S. Perkin I*, 858 (1980).

¹⁴⁸ G. C. Crockett and T. H. Koch, *J. Org. Chem.* **42**, 2721 (1977).

¹⁴⁹ P. Y. Johnson, C. E. Hatch, and N. R. Schmuff, *J. C. S. Chem. Commun.*, 725 (1975).

¹⁵⁰ R. Hunt and S. T. Reid, *J. C. S. Perkin I*, 2527 (1972).

proposed to account for the formation of the triazolone **203** from the mesoionic 1,2,4-triazol-3-ones **204**.¹⁵¹ The photorearrangement of certain *N*-acylsydnone imines has also been described,¹⁵² and irradiation of

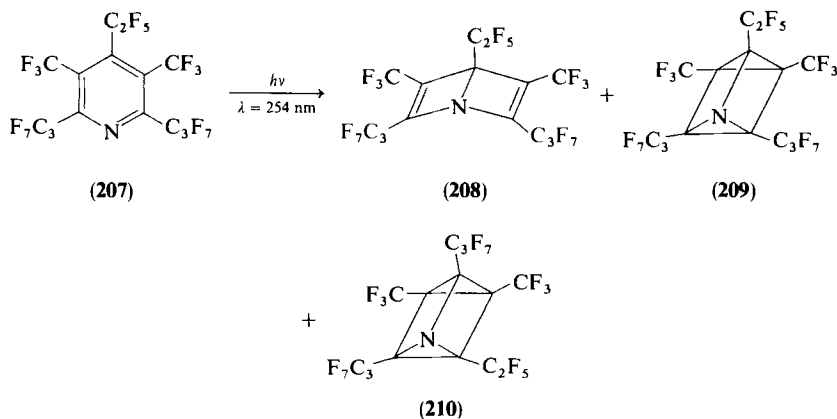


anhydro-5-hydroxythiazolium and -oxazolium hydroxides (**205**) results in ring opening and the formation of heterocumulenes (**206**).¹⁵³

¹⁵¹ H. Kato, T. Shiba, E. Kitajima, T. Kiyosawa, F. Yamada, and T. Nishiyama, *J. C. S. Perkin I*, 867 (1976).

¹⁵² A. Chinone and M. Ohta, *Chem. Lett.*, 969 (1972).

¹⁵³ N. H. Toubro, B. Hansen, N. Harrit, A. Holm, and K. T. Potts, *Tetrahedron* **35**, 229 (1979).



Ring transposition processes are well established in six-membered heteroaromatic systems. Recent studies have centered on perfluoro systems in which bicyclic and tricyclic intermediates are sufficiently stable to permit isolation or at least detection. Thus, on irradiation in $\text{CF}_2\text{ClCFCl}_2$, the perfluoropyridine **207** is converted into the azabicyclo[2.2.0]hexa-2,5-diene **208** and the two azaprismanes **209** and **210**.¹⁵⁴ An azabicyclo[2.2.0]hexa-2,5-diene has also been shown to be an intermediate in the photorearrangement of substituted 2-methylpyridines to *o*-substituted anilines.¹⁵⁵ Diazabicyclo[2.2.0]hexa-2,5-dienes have similarly been shown to be intermediates in the conversion of fluorinated pyridazines (**211**) into the corresponding pyrazines (**212**)¹⁵⁶; the proposed pathway is outlined in Scheme 7. Photoproducts which are formally dimers of intermediate azetes have been obtained when analogous reactions are carried out in a flow system.¹⁵⁷

Bridging of a different type has been observed in 3-oxido-1-phenylpyridinium (**213**) which on irradiation in ethyl acetate affords the isomer **214** by way of a photochemically allowed disrotatory ring closure.¹⁵⁸ Similarly, stable diaziridines (**215**) have been isolated on irradiation of 3-oxidopyridazinium betaines (**216**).¹⁵⁹ Other related transformations in 2-alkylcinolinium-4-olates¹⁶⁰ and in 5-oxidopyridazinium betaines¹⁶¹ have been

¹⁵⁴ R. D. Chambers and R. Middleton, *J. C. S. Perkin I*, 1500 (1977).

¹⁵⁵ K. Takagi and Y. Ogata, *J. C. S. Perkin II*, 1148, 1980 (1977); Y. Ogata and K. Takagi, *J. Org. Chem.* **43**, 944 (1978).

¹⁵⁶ R. D. Chambers, J. R. Maslakiewicz, and K. C. Srivastava, *J. C. S. Perkin I*, 1130 (1975).

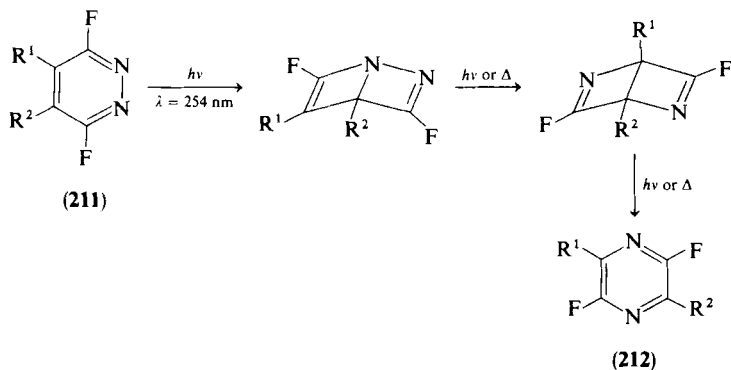
¹⁵⁷ R. D. Chambers and J. R. Maslakiewicz, *J. C. S. Chem. Commun.*, 1005 (1976).

¹⁵⁸ N. Dennis, A. R. Katritzky, and H. Wilde, *J. C. S. Perkin I*, 2338 (1976).

¹⁵⁹ Y. Maki, M. Kawamura, M. Okamoto, M. Suzuki, and K. Kenji, *Chem. Lett.*, 1005 (1977).

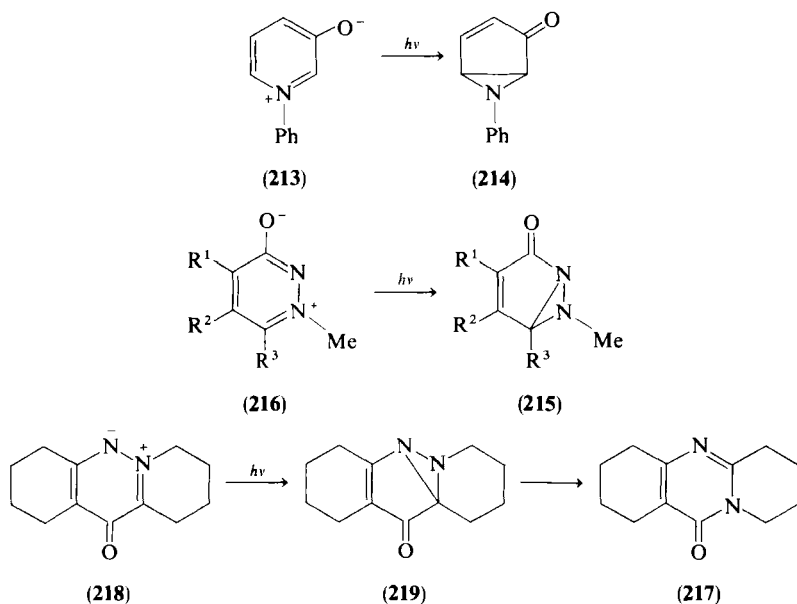
¹⁶⁰ D. E. Ames, S. Chandrasekhar, and R. Simpson, *J. C. S. Perkin I*, 2035 (1976).

¹⁶¹ Y. Maki, M. Suzuki, T. Furuta, M. Kawamura, and M. Kuzuya, *J. C. S. Perkin I*, 1199 (1979).



SCHEME 7

described, and the formation of the pyrimidone **217** from the pyridazinium 4-oxide **218** is believed to involve the diaziridine **219**.¹⁶²

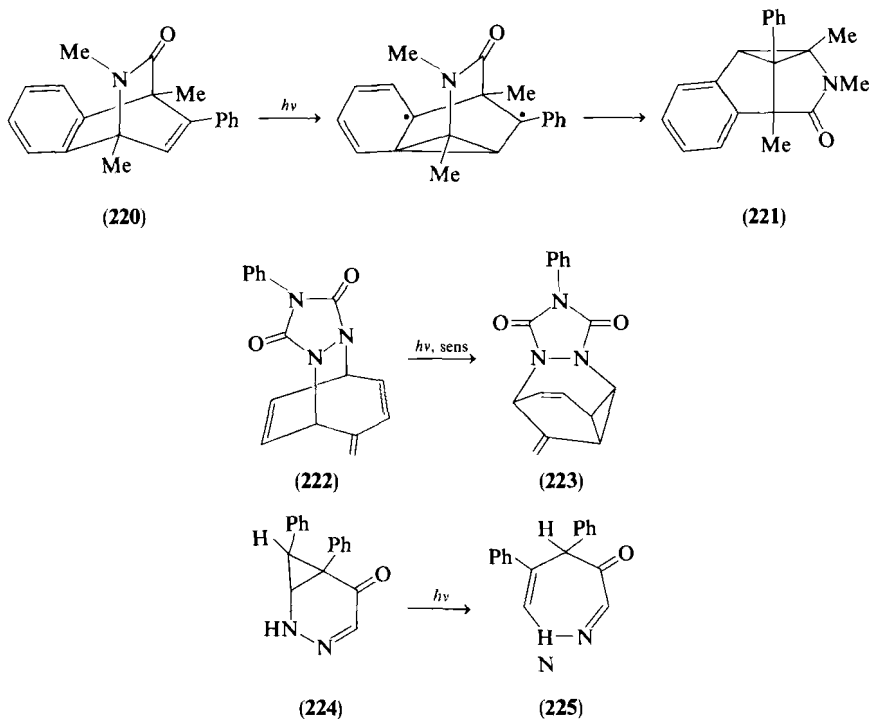


The possible involvement of bicyclic intermediates in the photorearrangement of hindered pyrid-4-ones to the corresponding pyrid-2-ones has been considered,¹⁶³ but the mechanism for the photochemical conversion of 4,6-dimethyl-1-(1'-piperidynyl)pyrid-2-one into the 3-piperidynyl isomer is less

¹⁶² R. Y. Ning, J. F. Blount, W. Y. Chen, and P. B. Madan, *J. Org. Chem.* **40**, 2201 (1972).

¹⁶³ N. Ishibe, S. Yutaka, J. Masui, and N. Ihda, *J. Org. Chem.* **43**, 2144 (1978).

clear.¹⁶⁴ The ring-fused dihydropyrid-2-one **220** undergoes photorearrangement to give a single product (**221**) via a pathway formally analogous to that of a di- π -methane rearrangement.¹⁶⁵ Mechanistically similar transformations have been reported in 4-substituted dihydropyrimidines¹⁶⁶ and in diazabicyclo[3.2.2]nona-3,8-diene (**222**),¹⁶⁷ the latter providing a synthetic entry into the diazabarbaralane system **223**. In contrast, 3(2*H*)-pyridazinones



on irradiation in methanol undergo a novel ring contraction to afford pyrrolin-2-ones,¹⁶⁸ whereas the 2,3-diazabicyclo[4.1.0]heptanone **224** is converted into the 1,5-dihydrodiazepinone **225**.¹⁶⁹

Various types of photochemically induced 1,3-shifts have been observed in nitrogen containing heterocycles. Concerted [1,3] suprafacial sigmatropic reactions are photochemically allowed processes, but many of the reported transformations especially those which arise by $n \rightarrow \pi^*$ excitation un-

¹⁶⁴ H. Furrer, *Tetrahedron Lett.*, 2953 (1974).

¹⁶⁵ M. Kuzuya, M. Ishikawa, T. Okuda, and H. Hart, *Tetrahedron Lett.*, 523 (1979).

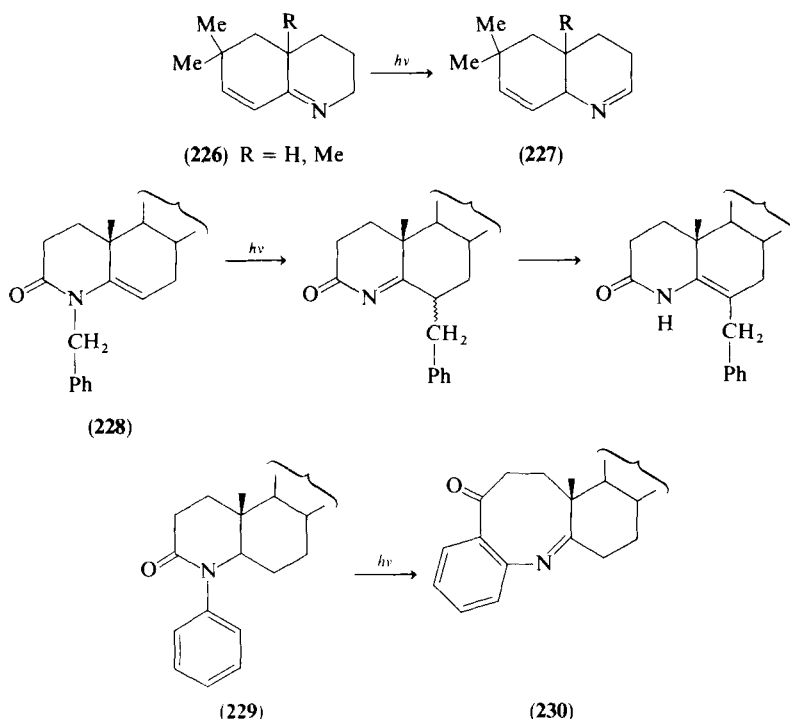
¹⁶⁶ R. E. van der Stoel and H. C. van der Plas, *J. C. S. Perkin I*, 1228 (1979).

¹⁶⁷ Z. Goldschmidt and Y. Bakal, *Tetrahedron Lett.*, 2809 (1974).

¹⁶⁸ T. Tsuchiya, M. Hasebe, H. Arai, and H. Igeta, *Chem. Pharm. Bull.* **22**, 2276 (1974).

¹⁶⁹ A. Nabeya, K. Kurita, and J. A. Moore, *J. Org. Chem.* **38**, 2954 (1973).

doubtedly proceed by way of radical intermediates. Double bond migration in the cyclic imine **226** to give the isomer **227** is the result of 1,3-hydrogen migration,¹⁷⁰ and a 1,3-benzyl migration has been observed in the steroidal enamide **228** on irradiation in tetrahydrofuran.¹⁷¹ 1,3-Acyl shifts are more common; examples include the photorearrangement of 2-benzoylisoquinolin-1(2*H*)one to the corresponding 4-benzoyl derivative¹⁷² and the photochemically induced ring expansion of the steroidal lactam **229** to the azocine **230**.¹⁷³ Related reactions such as the conversion of 2-alkyl-4-arylsulfonyloxypyrimidines on irradiation in cyclohexane into the corresponding sulfonylpyrimidines¹⁷⁴ and the formation of the quinazolines **231** and **232** by irradiation of the *N*-(dihydroquinazolinyl)carbamate **233** in ethanol¹⁷⁵ have been reported.



¹⁷⁰ P. Margaretha, *Helv. Chim. Acta* **61**, 1025 (1978).

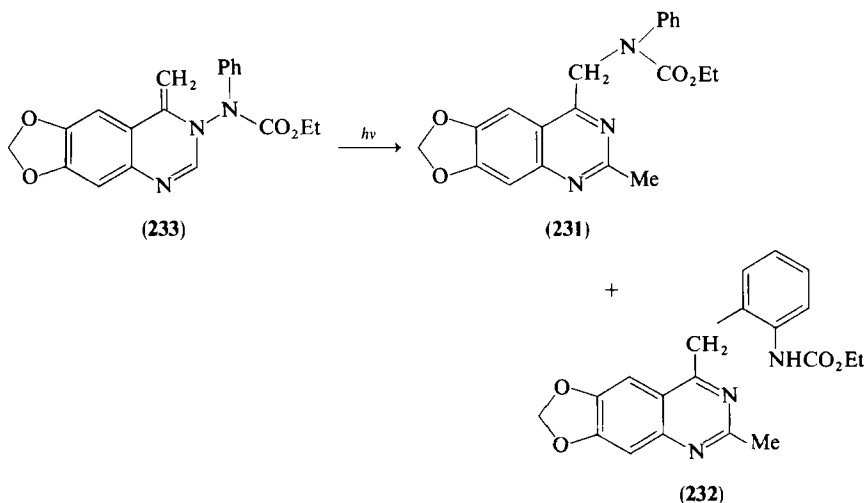
¹⁷¹ R. P. Gandhi, M. Singh, Y. P. Sachdeva, and S. M. Mukherji, *Chem. Ind. (London)*, 382 (1973).

¹⁷² R. W. Hoffmann and K. R. Eicken, *Chem. Ber.* **102**, 2987 (1969).

¹⁷³ R. P. Gandhi, M. Singh, Y. P. Sachdeva, and S. M. Mukherji, *Tetrahedron Lett.*, 661 (1973).

¹⁷⁴ R. Nasielski-Hinkens, J. Maeck, and M. Ten Voorde, *Tetrahedron* **28**, 5025 (1972).

¹⁷⁵ J. Fetter, K. Lempert, and J. Møller, *Tetrahedron* **34**, 2557 (1978).



3. Medium- and Large-Ring Heterocycles

The photochemistry of medium- and large-ring, nitrogen-containing heterocycles has been less systematically investigated, but a number of reactions are sufficiently general to warrant discussion. *Z* → *E* isomerization has been described in rings of this size; thus, *Z*-1,2-diazacyclo-oct-1-ene is converted on irradiation into the *E*-isomer in 60% yield.¹⁷⁶ Irradiation of *E*-tetrahydrothiadiazepin 1,1-dioxide (**234**) similarly gave the *Z*-isomer,¹⁷⁷ and the binding efficiency of an azobenzene-bridged azacrown ether for alkali metal ions can be modified by *E* → *Z* photoisomerization.¹⁷⁸

The first synthesis of 9-azabicyclo[6.1.0]nona-2,4,6-triene (**235**) has been achieved by irradiation of 1*H*-azonine (**236**) at 0°C.¹⁷⁹ An oxonin structure (**237**) has tentatively been assigned to the labile photoproduct of the azonine 1,2-oxide **238**.¹⁸⁰

Rearrangements arising by photochemically induced 1,3-acyl migrations have been reported in the 3*H*-azepine **239**,¹⁸¹ and in certain 1,3-dihydro-2*H*-

¹⁷⁶ C. G. Overberger, M. S. Chi, D. G. Pucci, and J. A. Barry, *Tetrahedron Lett.*, 4565 (1972).

¹⁷⁷ H. Lind, G. Rihs, and G. Rist, *Tetrahedron Lett.*, 339 (1980).

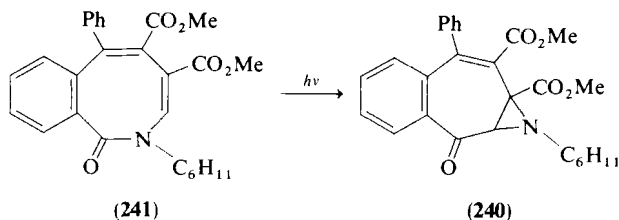
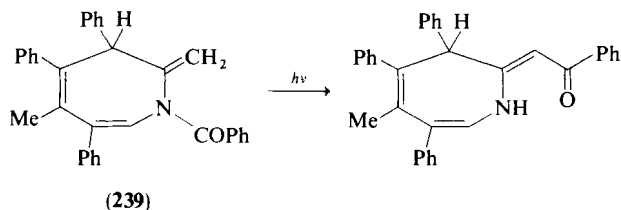
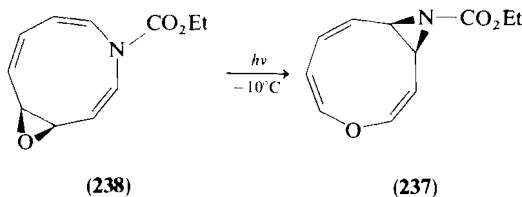
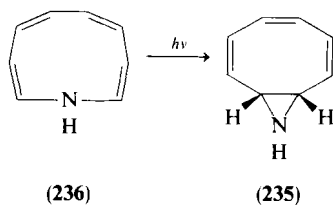
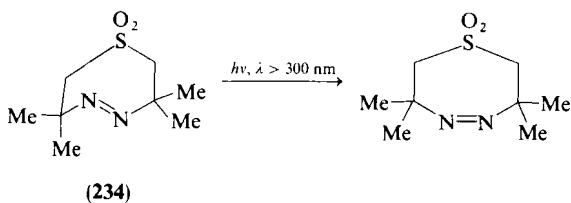
¹⁷⁸ S. Shinkai, T. Ogawa, T. Nakaji, Y. Kusano, and O. Manabe, *Tetrahedron Lett.*, 4569 (1979).

¹⁷⁹ A. G. Anastassiou, S. W. Eachus, R. L. Elliott, and E. Yakali, *J. C. S. Chem. Commun.*, 531 (1972).

¹⁸⁰ A. G. Anastassiou, S. J. Girgenti, R. C. Griffith, and E. Reichmanis, *J. Org. Chem.* **42**, 2651 (1977).

¹⁸¹ D. J. Anderson, A. Hassner, and D. Y. Tang, *J. Org. Chem.* **39**, 3076 (1974).

azepin-2-ones.¹⁸² The major product (**240**) of irradiation of *N*-cyclohexylbenzazocine (**241**) is at least formally the result of a 1,2-acyl migration.¹⁸³ The mechanism of the reported conversion of certain benzodiazepines into indole derivatives is uncertain.¹⁸⁴



¹⁸² H.-D. Becker and A. B. Turner, *Tetrahedron Lett.*, 4871 (1979).

¹⁸³ A. Padwa, P. Sackman, E. Shefter, and E. Vega, *J. C. S. Chem. Commun.*, 680 (1972).

¹⁸⁴ M. Steinman and Y.-S. Wong, *Tetrahedron Lett.*, 2087 (1974).

III. Photoaddition

A. PHOTOCYCLOADDITION TO HETEROCYCLES

Numerous examples of intermolecular and intramolecular photocycloaddition to heterocyclic systems (including the dimerization of individual heterocycles) have now been reported. Two types of cycloaddition can readily be effected photochemically, namely, $[\pi 2 + \pi 2]$ and $[\pi 4 + \pi 4]$ additions. Although concerted suprafacial additions of this type are allowed photochemical processes, in reality many cycloadditions occur via diradicals, zwitterions or exciplexes.

1. $[\pi 2 + \pi 2]$ Cycloadditions

$[\pi 2 + \pi 2]$ Cycloadditions are in general an effective way of constructing cyclobutane rings. A wide variety of heterocyclic systems dimerize in this way. 1,3-Diacetylindole, for example, affords the head-to-tail dimer **242** on irradiation in ethanol.¹⁸⁵ Ethyl 2-ethoxy-1,2-dihydroquinoline-1-carboxylate is similarly converted in diethyl ether into the trans head-to-head dimer.¹⁸⁶ Notable among many analogous photodimerizations are those reported in 1,4-dihydropyridines,¹⁸⁷ in furo[3,2-*b*]pyridin-2(4*H*)-ones,¹⁸⁸ in 8-methyl-*s*-triazolo[4,3-*a*]pyridine,¹⁸⁹ and in 2*H*-2-benzazepine-1,3-diones.¹⁹⁰ The $[\pi 2 + \pi 2]$ dimerization of amidopyrine is the first reported example of a photocycloaddition in a 4-pyrazolin-3-one.¹⁹¹

The photodimerization of pyrimidine bases continues to attract attention, undoubtedly because of the biological implications of such transformations. 1,3-Dimethyluracil affords four $[\pi 2 + \pi 2]$ dimers on irradiation in an ice-matrix.¹⁹² Analogous dimeric species have been obtained under a variety of conditions from dimethylthymine,¹⁹³ tetramethyluracil,¹⁹⁴ 5-methyloro-

¹⁸⁵ T. Hino, M. Taniguchi, T. Date, and Y. Iidaka, *Heterocycles* **7**, 105 (1977).

¹⁸⁶ M. Ikeda, S. Matsugashita, and Y. Tamura, *Chem. Pharm. Bull.* **24**, 1400 (1976).

¹⁸⁷ O. Mitsunobu, S. Matsumoto, M. Wada, and H. Masuda, *Bull. Chem. Soc. Jpn.* **45**, 1453 (1972).

¹⁸⁸ G. Jones and J. R. Phipps, *J. C. S. Perkin I*, 458 (1975).

¹⁸⁹ K. T. Potts, E. G. Brugel, and W. C. Dunlap, *Tetrahedron* **33**, 1247 (1977).

¹⁹⁰ M. S. Puar and B. R. Vogt, *Tetrahedron* **34**, 2887 (1978).

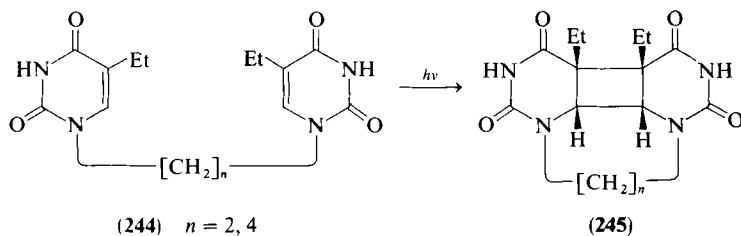
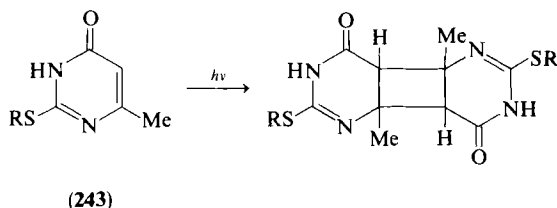
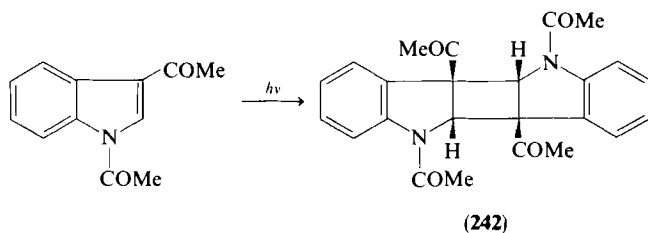
¹⁹¹ J. Reisch and M. Abdel-Khalek, *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **34B**, 1431 (1979).

¹⁹² E. Fahr, G. Fuerst, P. Maul, and H. Wieser, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **27B**, 1475 (1972).

¹⁹³ R. Kleopfer and H. Morrison, *J. Am. Chem. Soc.* **94**, 255 (1972).

¹⁹⁴ J. C. Otten, C. S. Yeh, S. Bryn, and H. Morrison, *J. Am. Chem. Soc.* **99**, 6353 (1977).

tate,¹⁹⁵ cytosine and methyl-substituted cytosines,¹⁹⁶ 5-fluorouracil,¹⁹⁷ and the 2-alkylthio-6-methyluracils **243**.¹⁹⁸ Polymethylene chains have been employed to study intramolecular photocycloaddition reactions of nucleic acid bases.¹⁹⁹ 1,1'-Di- and 1,1'-tetramethylenebis-5-ethyluracils **244** gave the *cis,syn*-adducts **245** on irradiation in aqueous acetone.²⁰⁰ The efficiency of such processes is dependent on polymethylene chain length.²⁰¹ The study has been extended to include 3,3'-, 1,3'-, and 1,5'-polymethylenebisthymines²⁰²; thus, the 1,5'-bisthymines **246** are converted in a similar fashion into the intramolecular adducts **247**.



¹⁹⁵ C. P. Huber, C. I. Birnbaum, M. L. Post, E. Kulikowska, L. Gajewska, and D. Shugar, *Can. J. Chem.* **56**, 824 (1978).

¹⁹⁶ H. Taguchi, B.-S. Hahn, and S. Y. Wang, *J. Org. Chem.* **42**, 4127 (1977).

¹⁹⁷ S. C. Shim and S. H. Lee, *Photochem. Photobiol.* **29**, 1035 (1979).

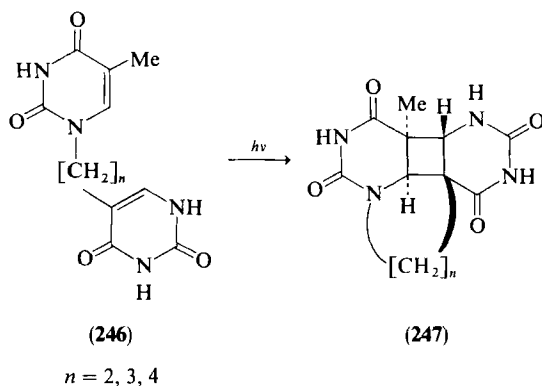
¹⁹⁸ K. Golankiewicz, M. Szajda, and E. Wyrzykiewicz, *Pol. J. Chem.* **53**, 529 (1979).

¹⁹⁹ K. Golankiewicz, *Heterocycles* **7**, 429 (1977).

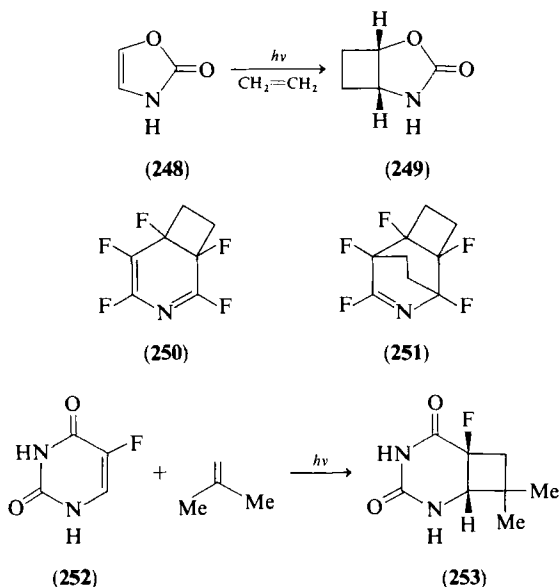
²⁰⁰ K. Golankiewicz and H. Koroniak, *Rocz. Chem.* **50**, 2041 (1976).

²⁰¹ H. Koroniak and K. Golankiewicz, *Pol. J. Chem.* **52**, 1567 (1978).

²⁰² N. J. Leonard and R. L. Cundall, *J. Am. Chem. Soc.* **96**, 5904 (1974).



Reports of $[\pi 2 + \pi 2]$ cycloaddition of nitrogen containing heterocycles to alkenes are so numerous that attention can be drawn here to only a few. Recent examples include the acetone-sensitized photoaddition of 4-oxazolin-2-one (248) to ethylene to give the cis-adduct 249,²⁰³ the photocycloadditions of N-substituted imidazoles to acrylonitrile²⁰⁴ and of N-methyl-4-hydroxyquinol-2-one to cyclohexene,²⁰⁵ and the photoaddition of pentafluoropyridine to ethylene to give the 1:1- and 1:2-adducts 250 and 251,



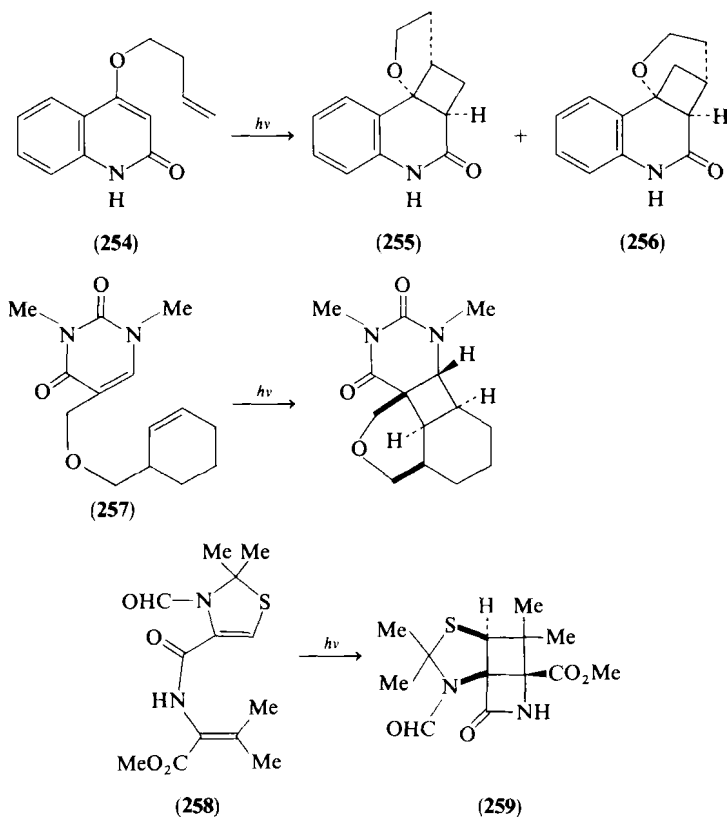
²⁰³ W. Hartmann, K.-H. Scholz, and H.-G. Heine, *Chem. Ber.* **113**, 1884 (1980).

²⁰⁴ Y. Ito and T. Matsuura, *J. Org. Chem.* **44**, 41 (1979).

²⁰⁵ R. G. Hunt, C. J. Potter, S. T. Reid, and M. L. Roantree, *Tetrahedron Lett.*, 2327 (1975).

respectively.²⁰⁶ In other additions, the fluoro substituent has been found to have a significant effect in controlling regioselectivity. 5-Fluorouracil (**252**), contrast to uracil and thymine, exhibits regioselectivity in the acetone-sensitized addition to 2-methylpropene to give the cyclobutane **253**.²⁰⁷

Intramolecular [$\pi 2 + \pi 2$] photocycloadditions are equally numerous and many have considerable synthetic potential. 4-(But-3-enyloxy)quinol-(1*H*)2-one (**254**), for example, is converted into a mixture of isomeric adducts **255** and **256** on irradiation in methanol.²⁰⁸ Intramolecular cycloaddition has also been observed in the pyrimidinedione **257**²⁰⁹ and in the dehydrovaline acrylamide **258** which on irradiation in dioxane affords the novel β -lactam system **259**.²¹⁰



²⁰⁶ M. G. Barlow, D. E. Brown, and R. N. Haszeldine, *J. C. S. Perkin I*, 363 (1978).

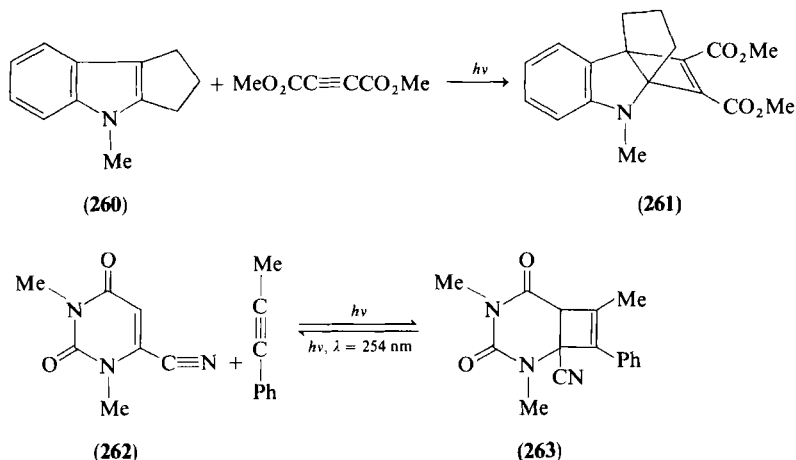
²⁰⁷ A. Wexler and J. S. Swenton, *J. Am. Chem. Soc.* **98**, 1602 (1976).

²⁰⁸ C. Kaneko, T. Naito, and M. Somei, *J. C. S. Chem. Commun.*, 804 (1979).

²⁰⁹ B. A. Pearlman, *J. Am. Chem. Soc.* **101**, 6398 (1979).

²¹⁰ P. K. Sen, C. J. Veal, and D. J. Young, *J. C. S. Chem. Commun.*, 678 (1977).

$[\pi 2 + \pi 2]$ Cycloaddition of nitrogen-containing heterocycles to alkynes with the formation of cyclobutenes is a much less common reaction. Reported examples include the photoaddition of the indole **260** to dimethyl acetylenedicarboxylate to give the highly colored 2-azatricyclo[3.3.2.0]deca-3,9-diene (**261**),²¹¹ and the photoaddition of 4-oxazolin-2-one to acetylene.²¹² 2:1-Adducts were, however, obtained on irradiation in acetone of 1,3-dimethyluracils and dimethyl acetylenedicarboxylate,²¹³ whereas irradiation of 6-cyano-1,3-dimethyluracil (**262**) in 1-phenylprop-1-yne affords the cyclobutene **263**.²¹⁴



2. $[\pi 4 + \pi 4]$ Cycloadditions

$[\pi 4 + \pi 4]$ Cycloadditions, although relatively rare, are not unknown in heterocyclic systems. The first documented example was the photodimerization of pyrid-2-one; a reinvestigation of this reaction has established that three other isomeric $[\pi 4 + \pi 4]$ dimers are formed in low yield in addition to the originally reported trans-anti dimer (**264**).²¹⁵ Attempts to effect analogous cycloadditions in a series of 1,1'-polymethylenedipyrid-2-ones were unsuccessful, $[\pi 2 + \pi 2]$ and $[\pi 4 + \pi 2]$ additions being preferred.²¹⁶ Thus,

²¹¹ P. D. Davis and D. C. Neckers, *J. Org. Chem.* **45**, 456 (1980).

²¹² K.-H. Scholz, H.-G. Heine, and W. Hartmann, *Tetrahedron Lett.*, 1467 (1978).

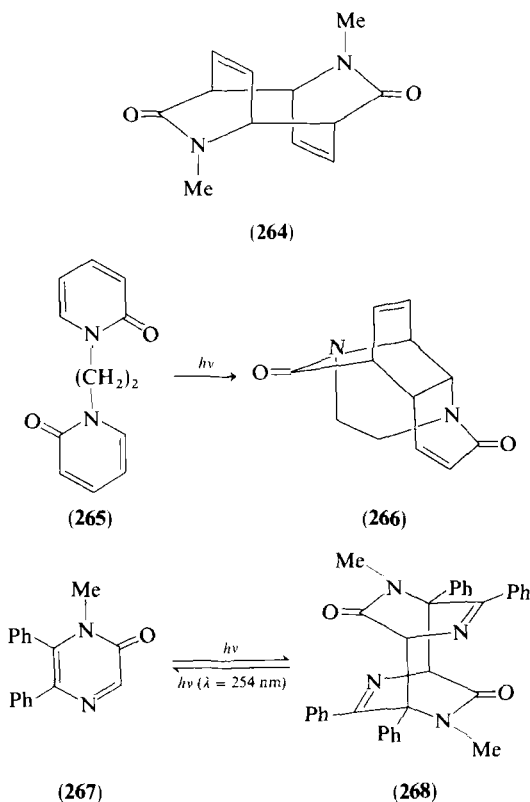
²¹³ T. Itoh, H. Ogura, N. Kawahara, and K. A. Watanabe, *Heterocycles* **12**, 1175 (1979).

²¹⁴ I. Saito, K. Shimozono, S. Miyazaki, T. Matsuura, K. Fukuyama, and Y. Katsube, *Tetrahedron Lett.*, 2317 (1980).

²¹⁵ Y. Nakamura, T. Kato, and Y. Morita, *J. C. S. Chem. Commun.*, 620 (1978).

²¹⁶ Y. Nakamura, J. Zsindely, and H. Schmid, *Helv. Chim. Acta* **59**, 2841 (1976).

the dipyrind-2-one **265** is converted on benzophenone-sensitized irradiation into the intramolecular adduct (**266**). [$\pi 4 + \pi 4$] Photodimerizations have also been observed in 5,6,7,8-tetrahydroquinol-2-one,²¹⁷ in *N*-methylisoin-dole,²¹⁸ and in 2-methyl-*s*-triazolo[1,5-*a*]pyridine.²¹⁹ A [$\pi 4 + \pi 4$] photo-adduct of 2-methyl-*s*-triazolo[1,5-*a*]pyridine with pyrid-2-one has also been reported.²²⁰ 1-Methyl-5,6-diphenylpyrazin-2-one (**267**) undergoes photodimerization in the solid state but not in solution.²²¹ The addition is reversed on irradiation of the photodimer **268** in methanol. This cleavage



reaction may therefore be responsible for the failure of this pyrazin-2-one and other related systems to undergo photodimerization in solution.

²¹⁷ J. N. Brown, R. L. R. Towns, and L. M. Trefonas, *J. Am. Chem. Soc.* **93**, 7012 (1971).

²¹⁸ W. Rettig and J. Wirz, *Helv. Chim. Acta* **61**, 444 (1978).

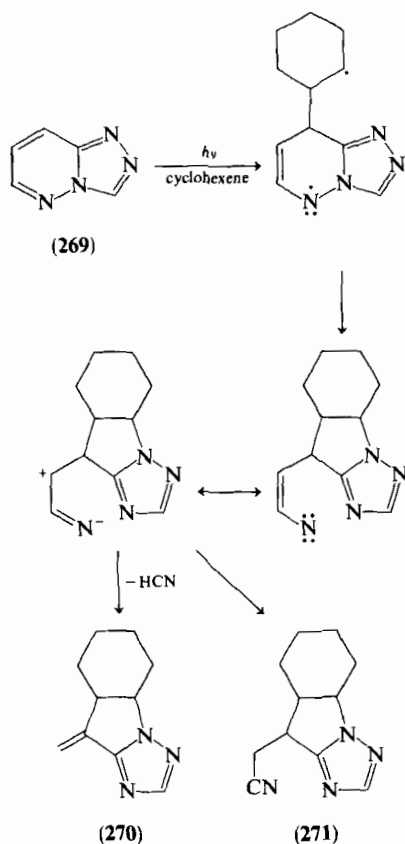
²¹⁹ T. Nagano, M. Hirobe, M. Itoh, and T. Okamoto, *Tetrahedron Lett.*, 3815 (1975).

²²⁰ T. Nagano, M. Hirobe, and T. Okamoto, *Tetrahedron Lett.*, 3891 (1977).

²²¹ T. Nishio, N. Nakajima, and Y. Omote, *Tetrahedron Lett.*, 2529 (1980).

3. Miscellaneous Cycloadditions

Photoproducts arising by a $[3 + 2]$ cycloaddition of *s*-triazolo[4,3-*b*]-pyridazine (**269**) to alkenes have been described.²²² Addition to cyclohexene, for example, led to the formation of adducts **270** and **271**, and the proposed mechanism is outlined in Scheme 8. The reaction has been extended to include addition to *cis*- and *trans*-hex-3-ene,²²³ cyclooctene,²²⁴ and furan.²²⁵



SCHEME 8

²²² J. S. Bradshaw, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **10**, 801 (1973).

²²³ J. T. Carlock, J. S. Bradshaw, and W. Zmolek, *Tetrahedron Lett.*, 2049 (1975).

²²⁴ J. S. Bradshaw, J. T. Carlock, and G. E. Maas, *J. Heterocycl. Chem.* **12**, 931 (1975).

²²⁵ G. E. Maas and J. S. Bradshaw, *J. Heterocycl. Chem.*, **14**, 81 (1977); J. S. Bradshaw, J. E. Tueller, S. L. Baxter, G. E. Maas, and J. T. Carlock, *ibid.*, 411.

B. SYNTHESIS OF HETEROCYCLES BY PHOTOADDITION

The synthesis of nitrogen containing heterocyclic systems by photocycloaddition processes is virtually limited to examples involving $[\pi 2 + \pi 2]$ cycloaddition of imines, nitriles, and azo compounds. Successful additions are few in number and the requirements for success uncertain. The reactions do not proceed with the facility with which carbonyl containing compounds undergo photocycloaddition to alkenes to give oxetans, and various explanations have been advanced to account for this observed lack of reactivity.²²⁶

The first undisputed cycloaddition of a carbon–nitrogen double bond to an alkene to give an azetidine was observed in 3-ethoxyisoindole (**272**)²²⁷; addition to cyclohexene takes place readily to give the adduct **273**, whereas with 2,3-dimethylbut-2-ene, the adduct **274** and the isomeric photoproducts **275** and **276** were obtained. Attempts to add 3-ethoxyisoindole to electron-deficient alkenes were unsuccessful. Analogous photoadditions to 1,3-dimethyl-6-azauracil,^{226,228} to 2,5-diphenyl-1,3,4-oxadiazole,²²⁹ and to the 1,3-oxazin-4-one **277**²³⁰ have been reported. The stable azetine **278** was obtained by thermal fragmentation of the adduct **279**. The first intramolecular addition of this type has been observed in a pyrimidine–purine dinucleotide analogue.²³¹ Pathways involving $[\pi 2 + \pi 2]$ cycloaddition to the carbon–nitrogen double bond and rearrangement in ketoimino ethers have been reviewed.²³²

An example of intramolecular addition of an azo group to an alkene has been described²³³; irradiation of azoalkene **280** affords an almost quantitative yield of the diazetidine **281** with no competing elimination of nitrogen. An analogous cycloaddition is thought to be implicated in the photoreaction of azobenzene with diketene.²³⁴

Reports of the photoaddition of nitriles to alkenes have also been published. An intermediate azetine **282** has been identified in the photoaddition of benzonitrile to 1,2-dimethylcyclohexene (**283**) to give adducts **284** and **285**,²³⁵ and stable azetines have been prepared by direct photoaddition of

²²⁶ J. S. Swenton and J. A. Hyatt, *J. Am. Chem. Soc.* **96**, 4879 (1974).

²²⁷ K. A. Howard and T. H. Koch, *J. Am. Chem. Soc.* **97**, 7288 (1975).

²²⁸ J. S. Swenton and R. J. Balchunis, *J. Heterocycl. Chem.* **11**, 453 (1974).

²²⁹ O. Tsuge, K. Oe, and M. Tashiro, *Tetrahedron* **29**, 41 (1973).

²³⁰ T. H. Koch, R. H. Higgins, and H. F. Schuster, *Tetrahedron Lett.*, 431 (1977).

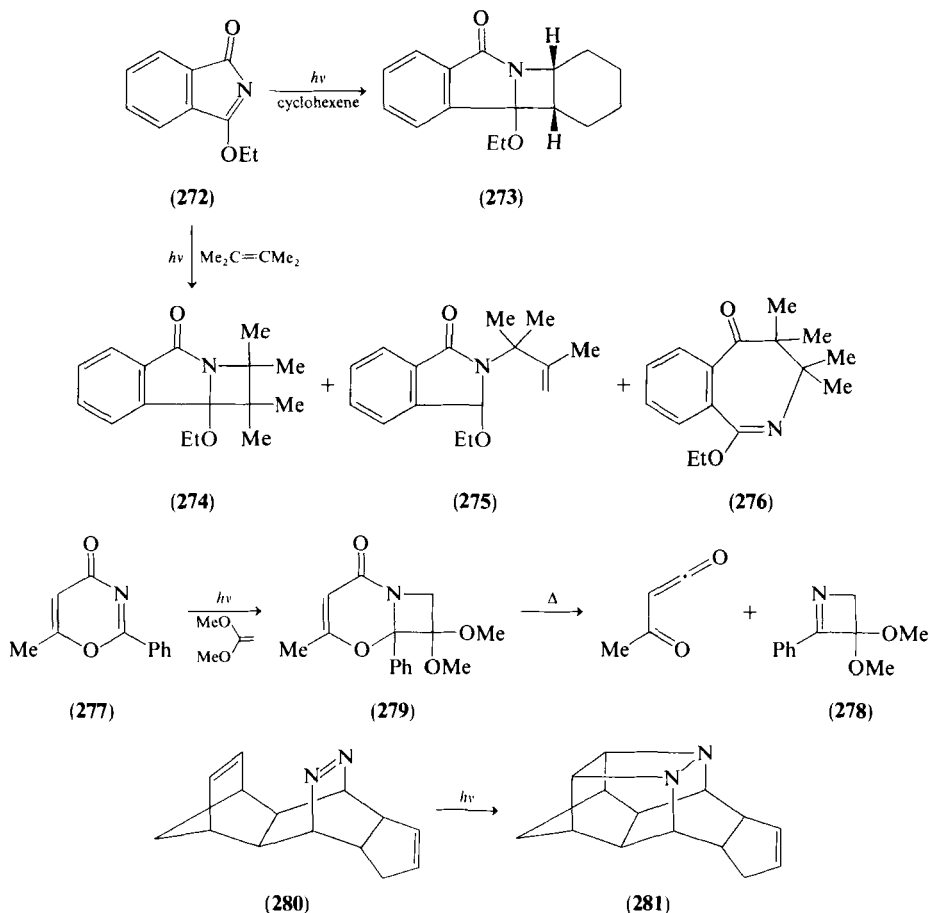
²³¹ S. Paszyc, B. Skalski, and G. Wenska, *Tetrahedron Lett.*, 449 (1976).

²³² T. H. Koch, D. R. Anderson, J. M. Burns, G. C. Crockett, K. A. Howard, J. S. Keute, R. M. Rodehorst, and R. J. Sluski, *Top. Curr. Chem.* **75**, 65 (1978).

²³³ W. Berning and S. Hünig, *Angew. Chem., Int. Ed. Engl.* **16**, 777 (1977).

²³⁴ T. Kato, M. Sato, and K. Tabei, *J. Org. Chem.* **39**, 3205 (1974).

²³⁵ T. S. Cantrell, *J. Org. Chem.* **42**, 4239 (1977).



aromatic nitriles to 2,3-dimethylbut-2-ene.²³⁶ An intermediate azetine (286) is also thought to be involved in the photoaddition of benzonitrile to 1,1-dimethoxy-2,2-dimethylethylene to give the 2-azabutadiene 287.²³⁷

N-Methylphthalimide (288) undergoes photoaddition in acetonitrile to *cis*-but-2-ene (289) to give *cis*-1,6,7-trimethyl-3,4-benzo-6,7-dihydroazepine-2,5-dione (290).²³⁸ Evidence supports a concerted [$\pi 2 + \sigma 2$] pathway to the intermediate 291. Similar additions to other alkenes have been reported.²³⁹ Electron transfer quenching has been shown to compete with cycloaddition

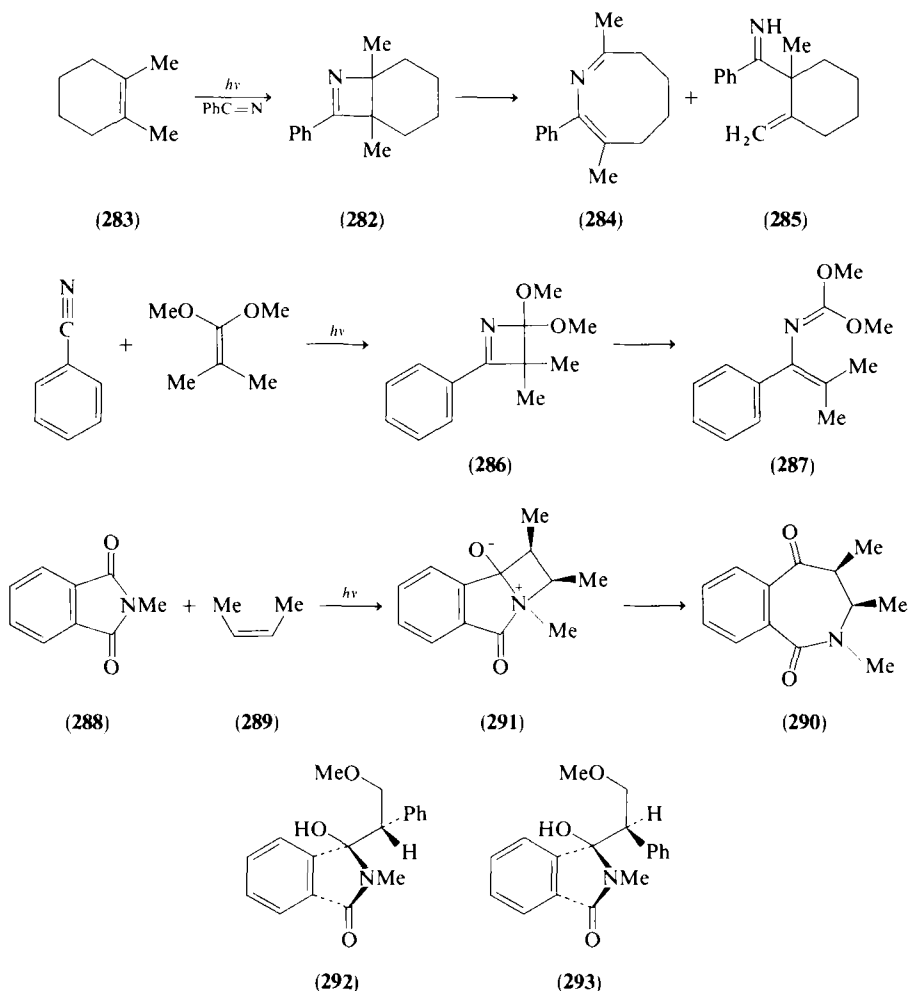
²³⁶ N. C. Yang, B. Kim, W. Chiang, and T. Hamada, *J. C. S. Chem. Commun.*, 729 (1976).

²³⁷ T. S. Cantrell, *J. Am. Chem. Soc.* **94**, 5929 (1972).

²³⁸ P. H. Mazzocchi, S. Minamikawa, and P. Wilson, *J. Org. Chem.* **44**, 1186 (1979).

²³⁹ P. H. Mazzocchi, S. Minamikawa, and K. J. Bowen, *J. Org. Chem.* **43**, 3079 (1978).

in some cases; thus, irradiation of *N*-methylphthalimide and styrene in methanol gave the solvent-incorporated adducts **292** and **293**, arising, it is thought, by trapping of a radical cation with methanol.²⁴⁰ The intramolecular equivalent of this process has been reported²⁴¹ and the reaction has been employed in the synthesis of macrocyclic compounds.²⁴²

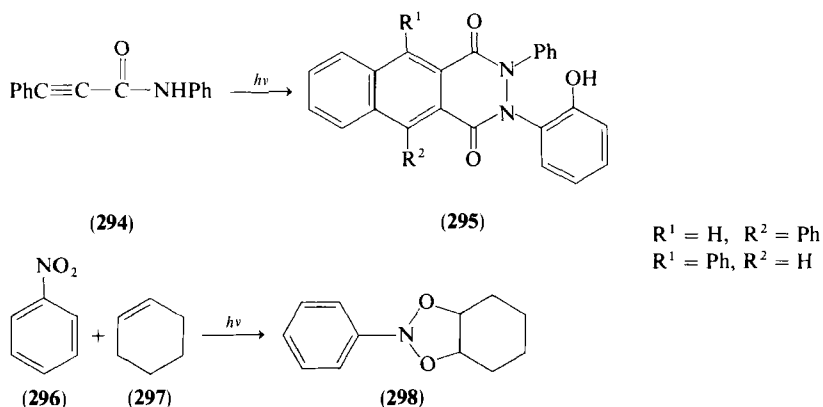


²⁴⁰ P. H. Mazzocchi, S. Minamikawa, and P. Wilson, *Tetrahedron Lett.*, 4361 (1978); K. Maruyama and Y. Kubo, *Chem. Lett.*, 851 (1978).

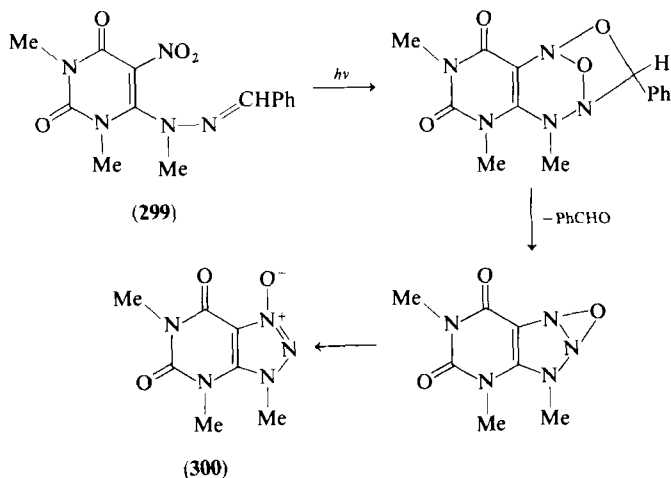
²⁴¹ K. Maruyama, Y. Kubo, M. Machida, K. Oda, Y. Karaoka, and K. Fukuyama, *J. Org. Chem.*, **43**, 2303 (1978).

²⁴² K. Maruyama and Y. Kubo, *J. Am. Chem. Soc.*, **100**, 7772 (1978).

The acetylenic amide **294** is converted on irradiation in benzene into two oxidized dimers **295**.²⁴³ A complex pathway involving a $[\pi 4 + \pi 2]$ cycloaddition followed by oxidation and photorearrangement has been proposed.



Full details of the $[3 + 2]$ photoaddition of nitrobenzene (**296**) to cyclohexene (**297**) to give the 1,3,2-dioxazole (**298**), stable at -70°C , have now been published.²⁴⁴ An analogous intramolecular cycloaddition has been proposed to account for the novel photocyclization of the nitroauracil **299** to the triazole **300** and the pathway is outlined in Scheme 9.²⁴⁵ A 2-azaallyl radical has been shown to be an intermediate in the photoaddition of benzo-



SCHEME 9

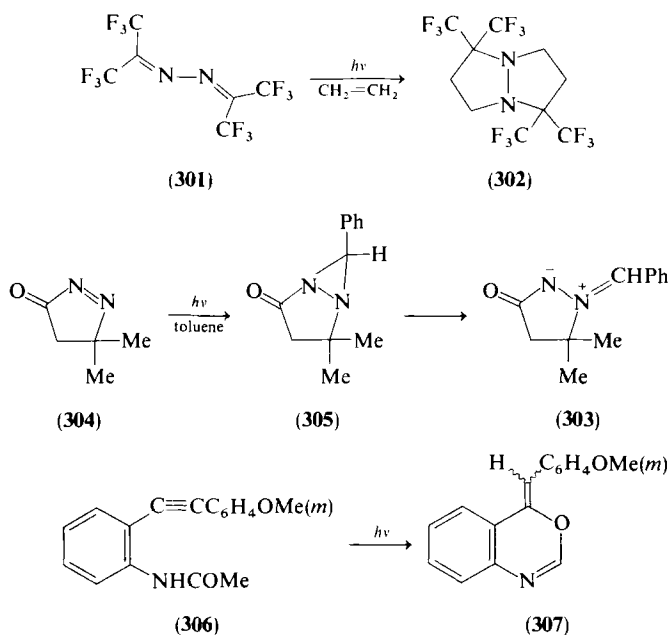
²⁴³ J. Reisch and D. H. Niemeyer, *Pharmazie* **27**, 458 (1972).

²⁴⁴ J. L. Charlton and P. de Mayo, *Can. J. Chem.* **46**, 1041 (1968).

²⁴⁵ Y. Maki, K. Izuta, and M. Suzuki, *Tetrahedron Lett.*, 1973 (1972).

phenone to an imine to give the corresponding oxazolidine.²⁴⁶ An unusual [3 + 3] photodimerization has been observed in a 3-pyrazolidone azomethine imine,²⁴⁷ and the photoaddition of hexafluoroacetoneazine (**301**) to ethylene is unexpectedly reported to give the bicycle **302**.²⁴⁸ The formation of the azomethine **303** from the 3-pyrazolidinone **304** by irradiation in toluene is claimed without any real evidence to involve the intermediate adduct **305**.²⁴⁹

Irradiation of *o*-acetamidophenylacetylene (**306**) in hexane or acetonitrile results in intramolecular addition and the formation of the benzoxazine **307**.²⁵⁰



C. PHOTOADDITION TO HETEROCYCLES

A wide variety of photoadditions to unsaturated nitrogen containing heterocyclic systems has been reported. It has, however, proved difficult to classify these processes as the reaction mechanisms involved have not always

²⁴⁶ A. A. Baum and L. A. Karnischky, *J. Am. Chem. Soc.* **95**, 3072 (1973).

²⁴⁷ M. Schulz, G. West, and R. Radeglia, *J. Prakt. Chem.* **318**, 955 (1976).

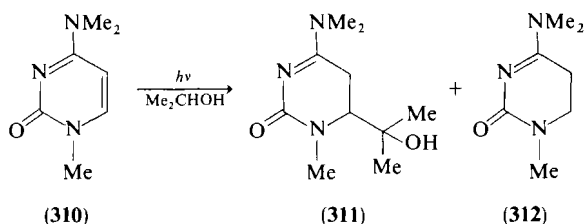
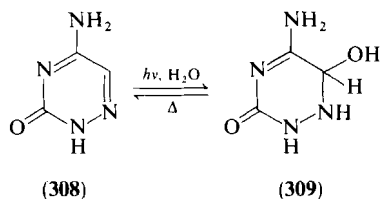
²⁴⁸ T. P. Fushaw and A. E. Tipping, *J. Chem. Soc. C*, 2404 (1971).

²⁴⁹ M. Schulz, *J. Prakt. Chem.* **315**, 711 (1973).

²⁵⁰ T. D. Roberts, L. Munchausen, and H. Schechter, *J. Am. Chem. Soc.* **97**, 3112 (1975).

been fully established; only the more thoroughly investigated additions will therefore be discussed in this article.

Two types of addition to pyrimidine bases appear to exist. The first, the formation of pyrimidine photohydrates, has been the subject of a detailed review.²⁵¹ Results suggest that two reactive species may be involved in the photohydration of 1,3-dimethyluracil.²⁵² A recent example of this type of addition is to be found in 6-azacytosine (**308**) which forms a photohydration product (**309**) analogous to that found in cytosine.²⁵³ The second type of addition proceeds via radical intermediates and is illustrated by the addition of propan-2-ol to the trimethylcytosine **310** to give the alcohol **311** and the dihydro derivative **312**.²⁵⁴ The same adduct is formed by a di-*tert*-butyl peroxide-initiated free radical reaction. Numerous other photoreactions involving the formation by hydrogen abstraction of hydroxyalkyl radicals and their subsequent addition to heterocycles have been reported. Systems studied include 3-aminopyrido[4,3-*e*]as-triazine,²⁵⁵ *O*²,2'-anhydrouridine,²⁵⁶ and *sym*-triazolo[4,3-*b*]pyridazine.²⁵⁷ The photoaddition of alcohols to purines is also a well-documented transformation. The stereospecific addition of methanol to the purine **313**, for example, is an important step in the synthesis of coformycin.²⁵⁸ These reactions are frequently more



²⁵¹ G. J. Fisher and H. E. Johns, *Photochem. Photobiol. Nucleic Acids* **1**, 169 (1976).

²⁵² J. G. Burr, C. Gilligan, and W. A. Summers, *Photochem. Photobiol.* **24**, 483 (1976).

²⁵³ L. Kittler, *Photochem. Photobiol.* **16**, 39 (1972).

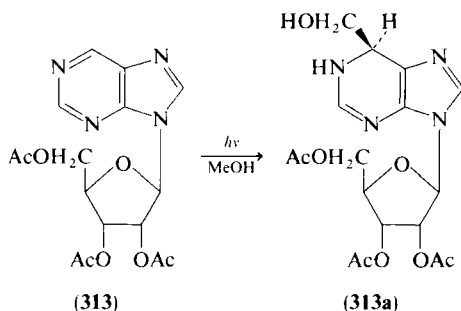
²⁵⁴ K. I. Ekpenyong and M. D. Shetlar, *Photochem. Photobiol.* **30**, 455 (1979).

²⁵⁵ P. Benko and L. Pallos, *Acta Chim. Acad. Sci. Hung.* **91**, 327 (1976).

²⁵⁶ K. K. Ogilvie and E. A. Thompson, *Photochem. Photobiol.* **24**, 81 (1976).

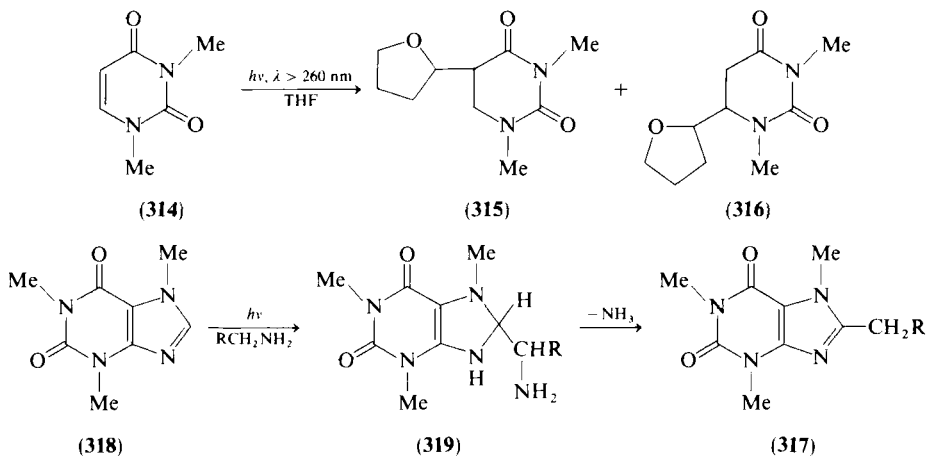
²⁵⁷ J. S. Bradshaw, M. Tišler, and B. Stanovnik, *J. Org. Chem.* **39**, 793 (1974).

²⁵⁸ M. Ohno, N. Yagisawa, S. Shibahara, S. Kondo, K. Maeda, and H. Umezawa, *J. Am. Chem. Soc.* **96**, 4326 (1974).



efficient in the presence of peroxide as a free radical initiator. Moreover, reaction is occasionally followed by elimination of water, thus resulting in a formal photoalkylation of the heterocyclic nucleus as reported, for example, in phenanthro[9,10-*d*]oxazole.²⁵⁹ The presence of acid has a profound effect on these transformations. This has been attributed either to the ability of the acid to promote dehydration in the initially formed alcohol or to ease of electron transfer to the protonated nitrogen heterocycle.²⁶⁰

Analogous photoadditions have been observed on irradiation of pyrimidine and purine bases in ethers and amines. Irradiation of 1,3-dimethyluracil (314) in tetrahydrofuran leads to the formation of 5- and 6-(tetrahydrofuran-2-yl)-5,6-dihydrouracils 315 and 316.²⁶¹ Similarly, solvent adducts arising by way of initial hydrogen abstraction have been obtained on irradiation of pyrazine derivatives in diethyl ether or tetrahydrofuran.²⁶² The



²⁵⁹ M. Maeda, M. Kawashige, and M. Kojima, *J. C. S. Chem. Commun.*, 511 (1977).

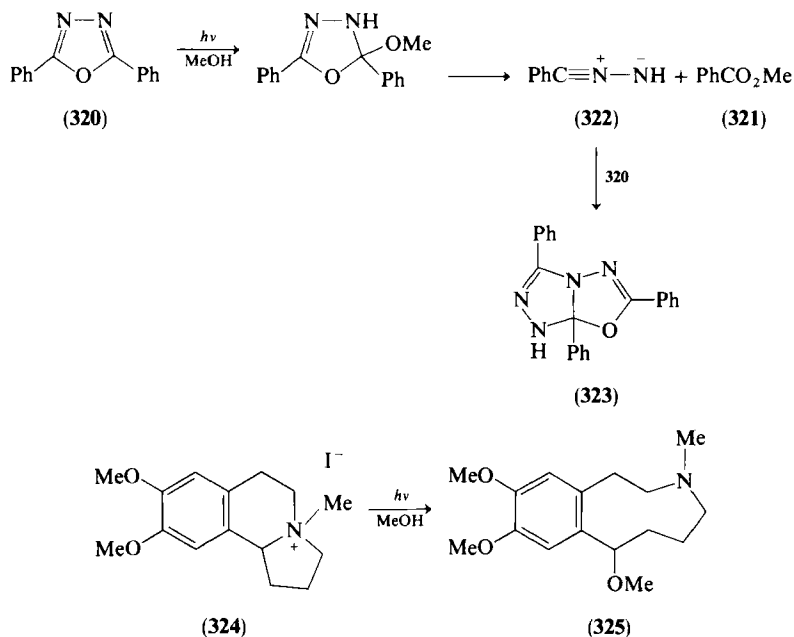
²⁶⁰ S. Wake, Y. Takayama, Y. Otsuji, and E. Imoto, *Bull. Chem. Soc. Jpn.* **47**, 1257 (1974).

²⁶¹ M. D. Shetlar, *J. C. S. Chem. Commun.*, 653 (1975).

²⁶² K. Yamada, K. Katsuura, H. Kasimura, and H. Iida, *Bull. Chem. Soc. Jpn.* **49**, 2805 (1976).

addition of amine is illustrated by the formation of 8-alkylated caffeines **317** on irradiation of caffeine (**318**) in the presence of primary amines²⁶³; the adduct **319** is believed to be an intermediate.

Many other miscellaneous additions of alcohols have been described. Polar addition of methanol to 2*H*-pyrroles²⁶⁴ and to azepines²⁶⁵ has been observed. Photoaddition of methanol to the 1,3,4-oxadiazole **320** is followed by cycloelimination of methyl benzoate (**321**) to give the ylid **322**.²⁶⁶ An adduct (**323**) of the ylid and the 1,3,4-oxadiazole has been isolated. Photoaddition of methanol to the quaternary ammonium salt **324** results in ring expansion and the formation of the azonine **325**.²⁶⁷



IV. Photocyclization

A variety of approaches to the synthesis of heterocycles by photocyclization have been reported. These will be considered under three headings.

²⁶³ A. Stankunas, I. Rosenthal, and J. N. Pitts, *Tetrahedron Lett.*, 4779 (1971); D. Elad and J. Salomon, *ibid.*, 4783.

²⁶⁴ J. M. Patterson, R. L. Beine, and M. R. Boyd, *Tetrahedron Lett.*, 3923 (1971).

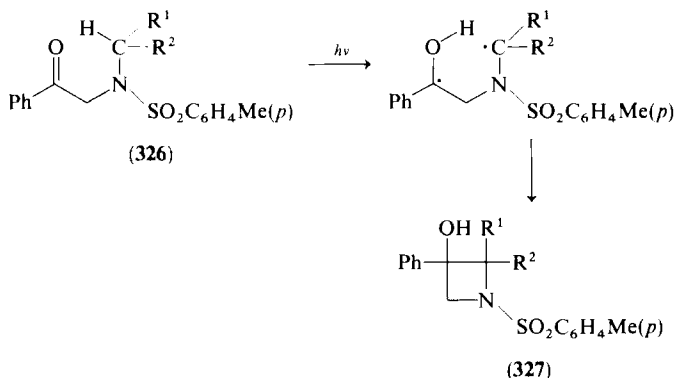
²⁶⁵ T. H. Koch, M. A. Geigel, and C.-C. Tsai, *J. Org. Chem.* **38**, 1090 (1973).

²⁶⁶ O. Tsuge, K. Oe, and M. Tashiro, *Chem. Lett.*, 1207 (1977).

²⁶⁷ J. B. Bremner and K. N. Winzenberg, *Chem. Ind. (London)*, 421 (1980).

A. NORRISH TYPE II CYCLIZATIONS

Norrish Type II photocyclizations have been employed in many instances in the synthesis of nitrogen heterocycles. Type II cyclizations are the result of an intramolecular hydrogen abstraction by an excited carbonyl group followed by cyclization of the resulting biradical. Hydrogen abstraction from the γ -carbon atom is normally preferred. The introduction of a nitrogen atom



into the alkyl chain provides a route to azetidinols. Aminoketones (326) are converted in this way on irradiation in diethyl ether into the azetidinols 327.²⁶⁸ Analogous azetidinol formation has been reported in 2-*N*-alkyl-*N*-arylamino-cyclohexanones²⁶⁹ and in *N,N*-dibenzyl- α -oxoamides (328; $\text{R}^1 = \text{Ph}$).²⁷⁰ In contrast, the corresponding *N,N*-dialkyl- α -oxoamides (328; $\text{R}^1 = \text{Me, Et}$) are converted in methanol to the oxazolidin-4-ones 329 by a pathway that is believed to involve an additional 1,4-hydrogen transfer. Two possible explanations are outlined in Scheme 10. The 3-carbomethoxy-6-hydroxypenamams 330 have been synthesised by photocyclization of the corresponding 2-oxoamides 331,²⁷¹ whereas the principal photoproduct of ethyl (–)-3-(oxophenylacetyl)thiazolidine-4-carboxylate is the oxazolidin-4-one which is formed in addition to the 6-hydroxypenam.²⁷² The formation of an azetidinone by irradiation of *N,N*-dibenzylmethacrylamide has unexpectedly been shown to involve dimethylketene and an imine as intermediates.²⁷³

²⁶⁸ E. H. Gold, *J. Am. Chem. Soc.* **93**, 2793 (1971).

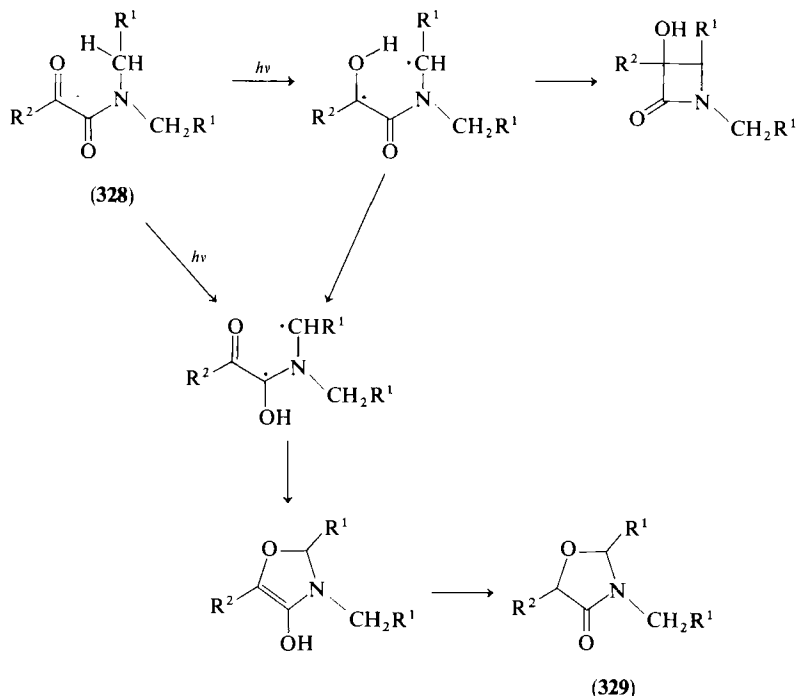
²⁶⁹ J. Hill and J. Townend, *J. C. S. Chem. Commun.*, 1108 (1972).

²⁷⁰ H. Aoyama, T. Hasegawa, M. Watabe, H. Shiraishi, and Y. Omote, *J. Org. Chem.* **43**, 419 (1978).

²⁷¹ K. R. Henery-Logan and C. G. Chen, *Tetrahedron Lett.*, 1103 (1973).

²⁷² N. G. Johansson, B. Åkermarck, and B. Sjöberg, *Acta Chem. Scand., Ser B* **B30**, 383 (1976).

²⁷³ H. Aoyama, T. Hasegawa, M. Okazaki, and Y. Omote, *J. C. S. Perkin I*, 263 (1979).



SCHEME 10

Intramolecular δ -hydrogen abstraction (1,6-hydrogen transfer) by an excited carbonyl is also a primary photochemical process, especially when γ -hydrogen abstraction is not possible. Thus, benzoylacetamide (332) is converted on irradiation in benzene to the pyrrolidin-2-one 333.²⁷⁴ An alternative mechanism involving electron transfer from nitrogen to singlet-excited carbonyl followed by proton transfer has been proposed. Similar photocyclizations have been reported in *N,N*-dialkyl-2-cycloalkanone-carboxamides,²⁷⁵ in *N,N*-dialkylacetoacetamides,²⁷⁶ and in the *N*-benzoylated Mannich bases 334 which are converted on irradiation into the pyrrolidinols 335.²⁷⁷

Systematic studies of the photoreactions of cyclic imides and in particular of phthalimide derivatives have been the subject of a review.²⁷⁸ One of the

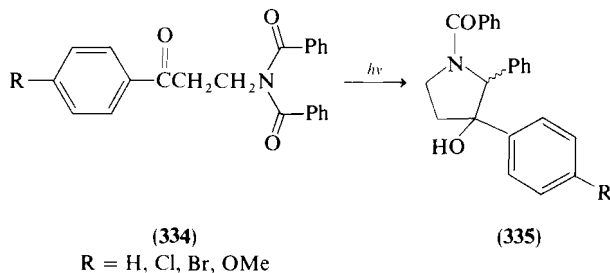
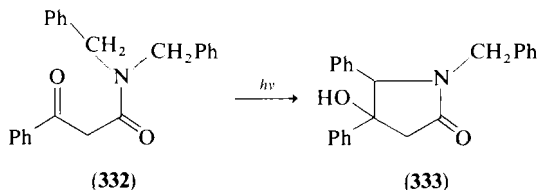
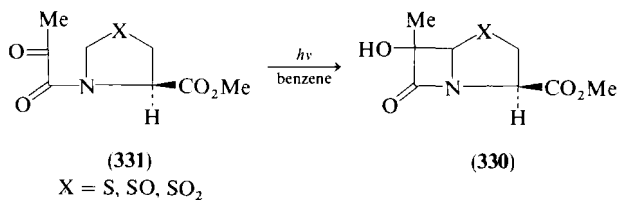
²⁷⁴ T. Hasegawa, H. Aoyama, and Y. Omote, *J. C. S. Perkin I*, 963 (1979).

²⁷⁵ T. Hasegawa, M. Inoue, H. Aoyama, and Y. Omote, *J. Org. Chem.* **43**, 1005 (1978).

²⁷⁶ T. Hasegawa, H. Aoyama, and Y. Omote, *J. C. S. Perkin I*, 2054 (1976).

²⁷⁷ H. G. Henning, T. Dietzsch, R. Groh, and T. Szabo, *Z. Chem.* **19**, 218 (1979).

²⁷⁸ Y. Kanaoka, *Acc. Chem. Res.* **11**, 407 (1978).



synthetically useful pathways in these systems is that involving Type II photocyclization. The first such example observed was the conversion of *N*-(*o*-tolyl)phthalimide (**336**) to the indolo[2,1-*a*]isoindoles **337** and **338**.²⁷⁹ γ -Hydrogen abstraction, however, is preferred in *N*-alkylphthalimides. An example of this type of behavior is to be found in the *N*-cycloalkylphthalimides **339** which are converted on irradiation to the azetidinols **340**; retro aldol ring expansion in this and other related systems affords benzazepines (**341**).²⁸⁰ Other *N*-substituted phthalimides undergo similar photocyclizations²⁸¹ as do *N*-substituted succinimides and glutarimides.²⁸²

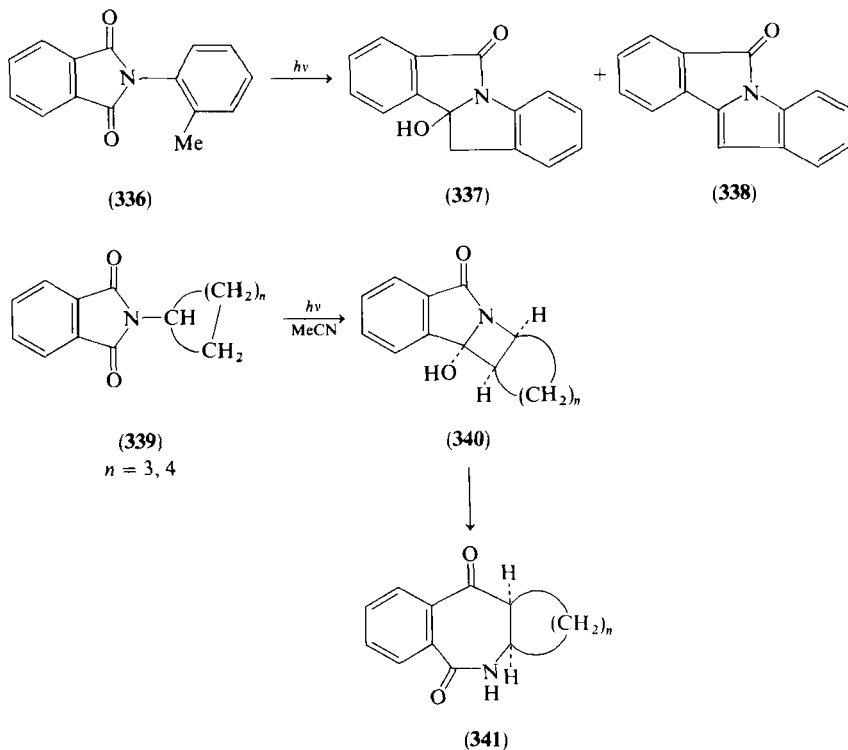
The presence of heteroatoms in the *N*-alkyl chain can significantly affect the cyclization process. Benzylic hydrogen abstraction is preferred, for

²⁷⁹ Y. Kanaoka, C. Nagasawa, H. Nakai, Y. Sato, H. Ogiwara, and T. Mizoguchi, *Heterocycles* **3**, 553 (1975).

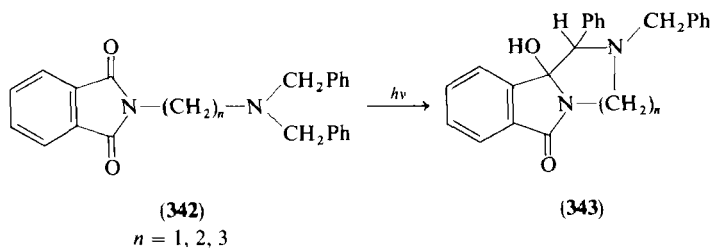
²⁸⁰ Y. Kanaoka, K. Koyama, J. L. Flippen, I. L. Karle, and B. Witcop, *J. Am. Chem. Soc.* **96**, 4719 (1974).

²⁸¹ Y. Kanaoka, Y. Migata, K. Koyama, Y. Sato, H. Nakai, and T. Mizoguchi, *Tetrahedron Lett.*, 1193 (1973).

²⁸² H. Nakai, Y. Sato, T. Mizoguchi, M. Yamazaki, and Y. Kanaoka, *Heterocycles*, **8**, 345 (1977); Y. Kanaoka, H. Okajima, and Y. Hatanaka, *ibid.*, 339.

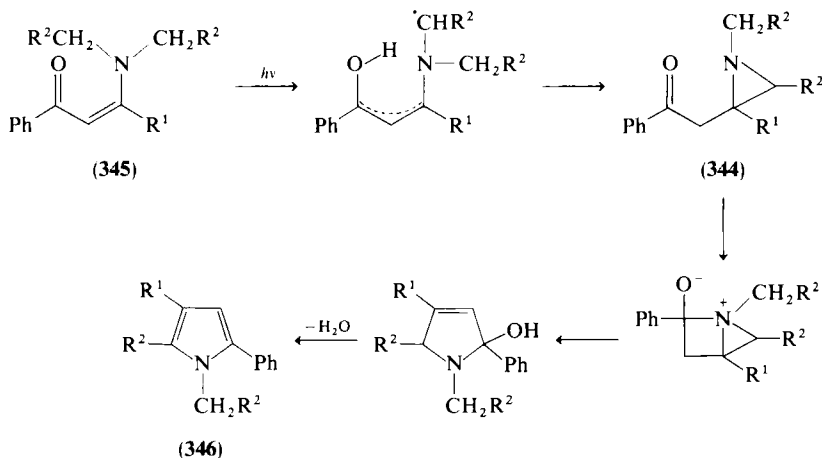


example, in the *N*-(dibenzylaminoalkyl)phthalimides **342** and gives a fused imidazoline (**343**; $n = 1$), a hexahydropyrazine (**343**; $n = 2$), and a hexahydro-1,4-diazepine (**343**; $n = 3$), respectively.²⁸³ Remote cyclization has been reported in *N*-(ω -methylanilino)alkylphthalimides and provides a useful route to nitrogen containing macrocycles.²⁸⁴ Evidence that an initial



²⁸³ J. D. Coyle and G. L. Newport, *Synthesis*, 381 (1979).

²⁸⁴ M. Machida, H. Takechi, and Y. Kanaoka, *Heterocycles* 7, 273 (1977).



electron transfer step is involved in these transformations has been presented.²⁸⁵

Intramolecular hydrogen abstraction leading to the aziridine **344** has been proposed to account for the unexpected conversion of the β -aminovinyl phenyl ketones **345** into the pyrroles **346**.²⁸⁶

B. PHOTOELIMINATION OF HX

Cyclization arising from the intramolecular photoelimination of HCl, HBr, and HI has been extensively used in the synthesis of heterocycles and alkaloids. The mechanisms of these transformations have not in many cases been thoroughly investigated. Some undoubtedly are initiated by simple homolysis of the carbon-halogen bond whereas others involve photocyclization and subsequent elimination of HX.

Representative of recent applications of the reaction to the synthesis of heterocycles are the photodehydrochlorination of chlorobenzo[*b*]thiophen (**347**) to give the fused pyrimidone **348**,²⁸⁷ the photoelimination of HI from iodobenzene derivatives **349** to give the benzazepines **350**,²⁸⁸ and the synthesis of the medium ring aza-heterocycle **351** by irradiation of the chloro precursor **352**.²⁸⁹ Included among the many other examples of

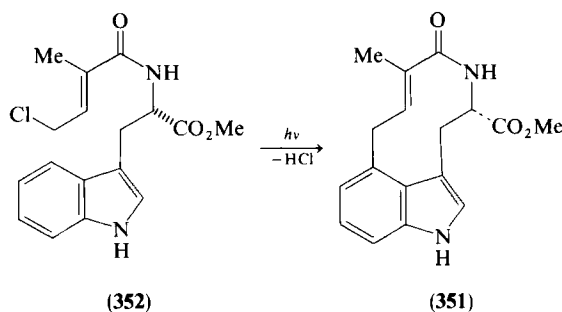
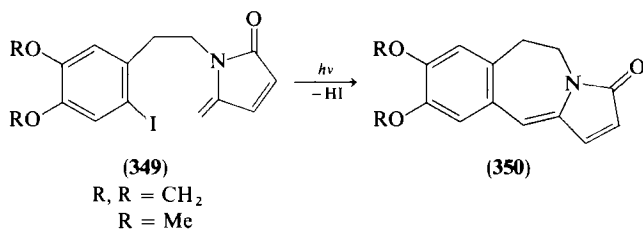
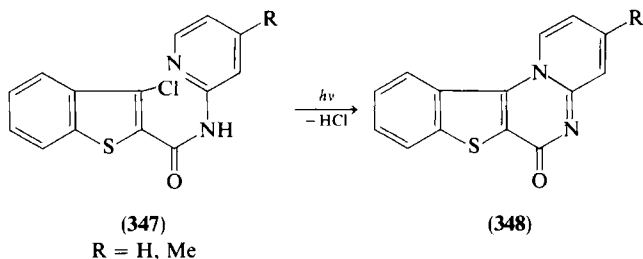
²⁸⁵ J. D. Coyle, G. L. Newport, and A. Harriman, *J. C. S. Perkin II*, 133 (1978).

²⁸⁶ H. Aoyama, T. Nishio, Y. Hirabayashi, H. Noda, and N. Sugiyama, *J. C. S. Perkin I*, 298 (1975).

²⁸⁷ M. Terashima, K. Seti, K. Itoh, and Y. Kanaoka, *Heterocycles* **8**, 421 (1977).

²⁸⁸ I. Tse and V. Snieckus, *J. C. S. Chem. Commun.*, 505 (1976).

²⁸⁹ N. G. Anderson and R. G. Lawton, *Tetrahedron Lett.*, 1843 (1977).



heterocyclic systems obtained in this way are 3,3a,4,5-tetrahydropyrrolo-[3,2,1-*de*]phenanthridine-1,7(2*H*)-dione,²⁹⁰ 2-methylbenzothiazole,²⁹¹ pyrazolo[1,5-*f*]phenanthridine,²⁹² and various benzazepines.²⁹³

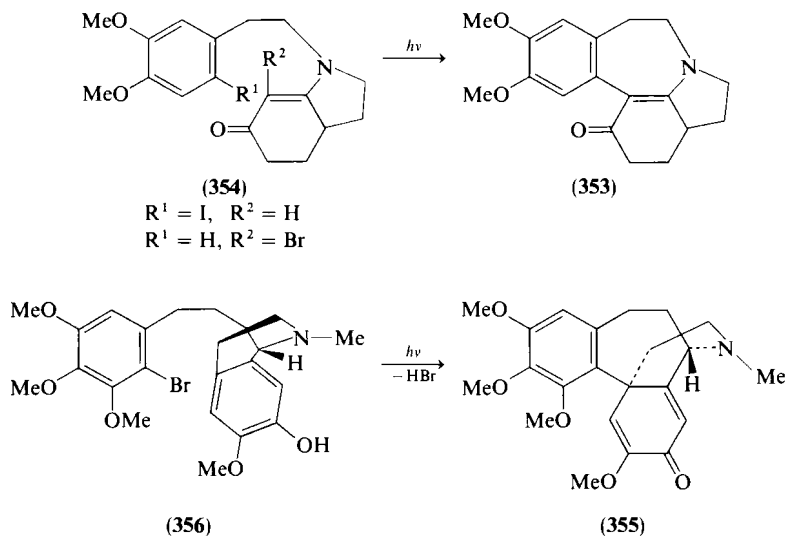
A wide variety of alkaloids have been synthesized by this procedure although in many cases the chemical yields are low. Hexahydroapoerysopine (353), for example, has been prepared by irradiation in dioxane of either the 6'-iodo or the 7-bromo derivative of 1,2,3,3a,4,5-hexahydro-*N*-(3,4-di-

²⁹⁰ H. Iida, Y. Yuasa, and C. Kibayashi, *J. C. S. Chem. Commun.*, 766 (1978).

²⁹¹ R. Paramasivan, R. Palaniappan, and V. T. Ramakrishnan, *J. C. S. Chem. Commun.*, 260 (1979).

²⁹² W. J. Begley, J. Grimshaw, and J. Trocha- Grimshaw, *J. C. S. Perkin I*, 2653 (1974).

²⁹³ H. Iida, Y. Yuasa, and C. Kibayashi, *Tetrahedron Lett.*, 3817 (1978); A. Marsili, V. Scartoni, I. Morelli, and P. Pierangeli, *J. C. S. Perkin I*, 959 (1977); H. Iida, S. Aoyagi, and C. Kibayashi, *ibid.*, 120; P. W. Jeffs, J. F. Hansen, and G. A. Brine, *J. Org. Chem.* **40**, 2883 (1975).



methoxyphenethyl)indol-6-one (**354**),²⁹⁴ and *O*-methylandrocymbine (**355**) has been obtained from the halo precursor **356**.²⁹⁵ Analogous photocyclizations have been employed in the synthesis of pontevedrine,²⁹⁶ atheroline,²⁹⁷ boldine,²⁹⁸ and many others, and the photochemical synthesis of isoquinoline alkaloids has been reviewed.²⁹⁹

The intramolecular photoelimination of HCl from *N*-chloroacetyl derivatives of suitable amines is a useful and versatile approach to the synthesis of azaheterocycles. The *N*-chloroacetyl derivative **357** has been converted in this way to 7-oxodesethylcatharanthine (**358**) in 55% yield.³⁰⁰ Investigations in this area have been particularly concerned with the *N*-chloroacetyl derivatives of benzylamines and phenethylamines; the *N*-chloroacetylbenzylamine **359** on irradiation affords the two 3-oxo-1,2,3,4-tetrahydroisoquinolines **360** and **361**.³⁰¹ Competing photocyclizations have been observed in the case of 1-[3-(chloroacetylamino)propyl]-3-methylindole (**362**) which is converted into three photoproducts, **363**, **364**, and **365**.³⁰²

²⁹⁴ H. Iida, T. Takarai, and C. Kibayashi, *J. Org. Chem.* **43**, 975 (1978).

²⁹⁵ T. Kametani, Y. Satoh, and K. Fukumoto, *J. C. S. Perkin I*, 2160 (1972).

²⁹⁶ L. Castedo, R. Estévez, J. M. Saa, and R. Suau, *Tetrahedron Lett.*, 2179 (1978).

²⁹⁷ T. Kametani, R. Nitadori, H. Terasawa, K. Takahashi, M. Ihara, and K. Fukumoto, *Tetrahedron* **33**, 1069 (1977).

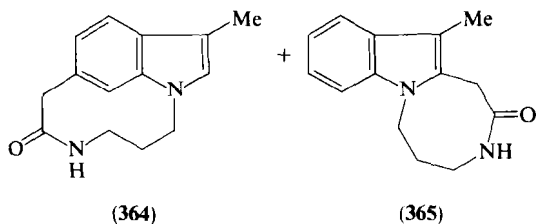
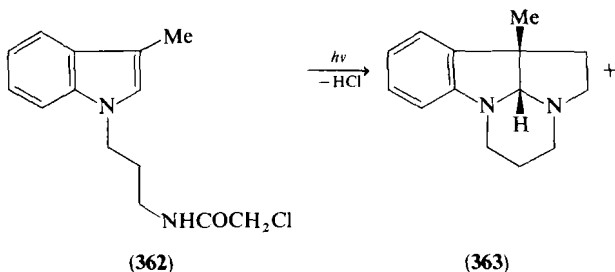
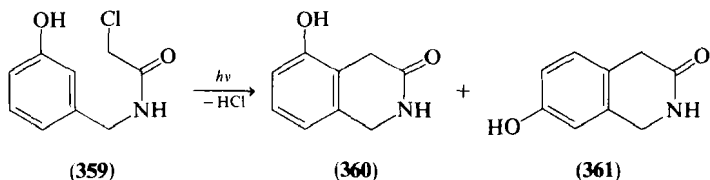
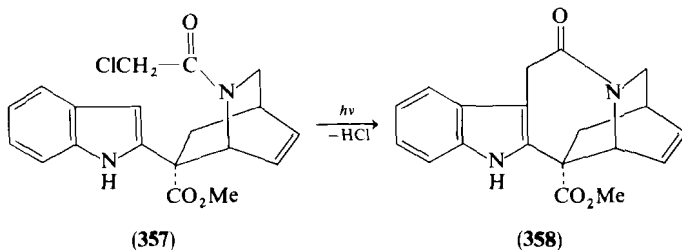
²⁹⁸ S. M. Kupchan, C.-K. Kim, and K. Miyano, *J. C. S. Chem. Commun.*, 91 (1976).

²⁹⁹ T. Kametani and K. Fukumoto, *Acc. Chem. Res.* **5**, 212 (1972).

³⁰⁰ R. J. Sundberg and J. D. Bloom, *Tetrahedron Lett.*, 5157 (1978).

³⁰¹ M. Ikeda, K. Hirao, Y. Okuno, N. Numao, and O. Yonemitsu, *Tetrahedron* **33**, 489 (1977).

³⁰² O. Schindler, P. Nilaus, U. Strauss, and H. P. Härter, *Helv. Chim. Acta* **59**, 2704 (1976).



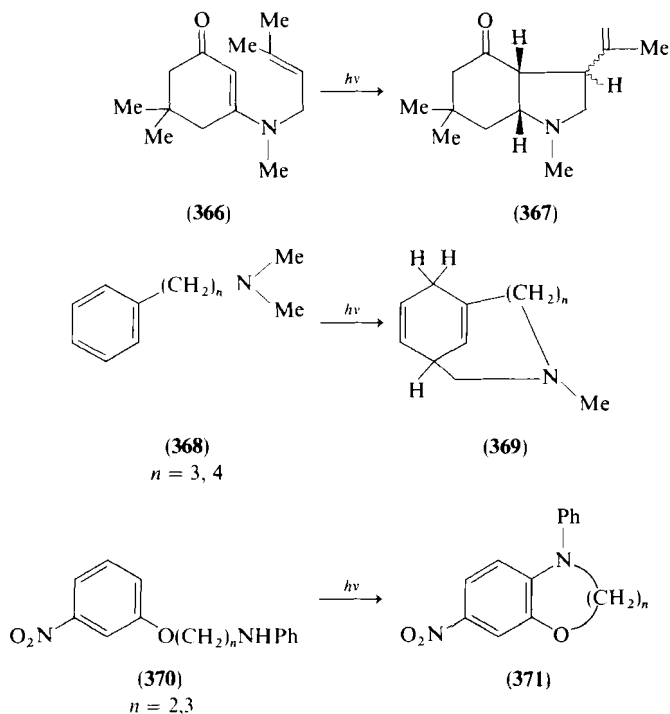
C. MISCELLANEOUS PHOTOCYCLIZATIONS

A wide variety of other photocyclizations have been reported, but only a few of these have any general application. The unsaturated amine **366** undergoes cyclization in cyclohexane to give the 7-azabicyclo[4.3.0]nonan-2-one **367**.³⁰³ The formation of pyrrolidine derivatives by photocyclization has also been observed in *N*-alkyl-2-allylanilines,³⁰⁴ and imidazoles have been obtained by irradiation of 2-amino-1-dialkylaminoanthraquinones.³⁰⁵

³⁰³ Y. Tamura, H. Ishibashi, and M. Ikeda, *J. Org. Chem.* **41**, 1277 (1976).

³⁰⁴ U. Koch-Pomeranz, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **58**, 178 (1975).

³⁰⁵ J. Lynch and O. Meth-Cohn, *J. C. S. Perkin I*, 920 (1973).



Intramolecular amine addition to benzene has been reported in the phenylalkylamines **368** to give the meta adducts **369** in low yield,³⁰⁶ whereas the [ω -(anilino)alkoxy]nitrobenzenes **370** undergo photocyclization in acetonitrile to give heterocycles **371**.³⁰⁷

The photocyclization of *cis*-diaminomaleonitrile (**372**) to 4-amino-5-cyanoimidazole (**373**) has been shown to proceed via the *trans* isomer **374**.³⁰⁸ 4-Amino-3-cyanopyrazole does not seem to be an intermediate in this transformation.³⁰⁹ Analogous cyclizations have been reported in the imidazole **373** which undergoes further photoreaction to yield the bicycle **375**, and in *o*-aminobenzonitrile which is converted into indazole.³¹⁰ This photocyclization has been extended to include enamionitriles **376**; spectroscopic evidence for the intermediacy of iminoketenimes **377** in this³¹¹ and other similar transformations³¹² have been reported.

³⁰⁶ D. Bryce-Smith, A. Gilbert, and G. Klunkin, *J. C. S. Chem. Commun.*, 330 (1973).

³⁰⁷ K. Mutai, S. Kanno, and K. Kobayashi, *Chem. Lett.*, 931 (1978).

³⁰⁸ T. H. Koch and R. M. Rodehorst, *J. Am. Chem. Soc.* **96**, 6707 (1974).

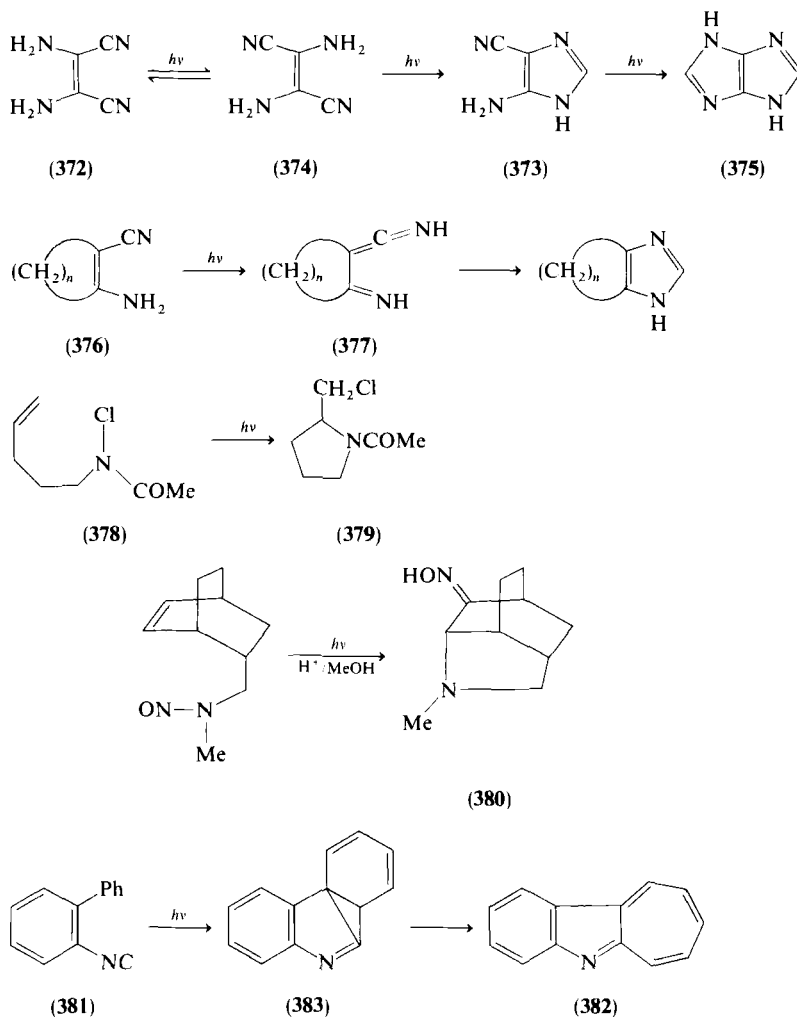
³⁰⁹ J. Kagan and B. Melnick, *J. Heterocycl. Chem.* **16**, 1113 (1979).

³¹⁰ J. P. Ferris and F. R. Antonucci, *J. C. S. Chem. Commun.*, 126 (1972).

³¹¹ J. P. Ferris and R. W. Trimmer, *J. Org. Chem.* **41**, 19 (1976).

³¹² J. P. Ferris, V. R. Rao, and T. A. Newton, *J. Org. Chem.* **44**, 4378, 4381 (1979).

New cyclizations via photochemically generated aminyl radicals have been reported, including further examples of the Hofmann–Loeffler–Freitag reaction.³¹³ Intramolecular addition of an aminyl radical, generated by photochemically induced nitrogen chlorine bond homolysis, is also accompanied by cyclization as illustrated by the conversion of the unsaturated *N*-chloroamide **378** to the pyrrolidine **379**.³¹⁴ Piperidine formation can also



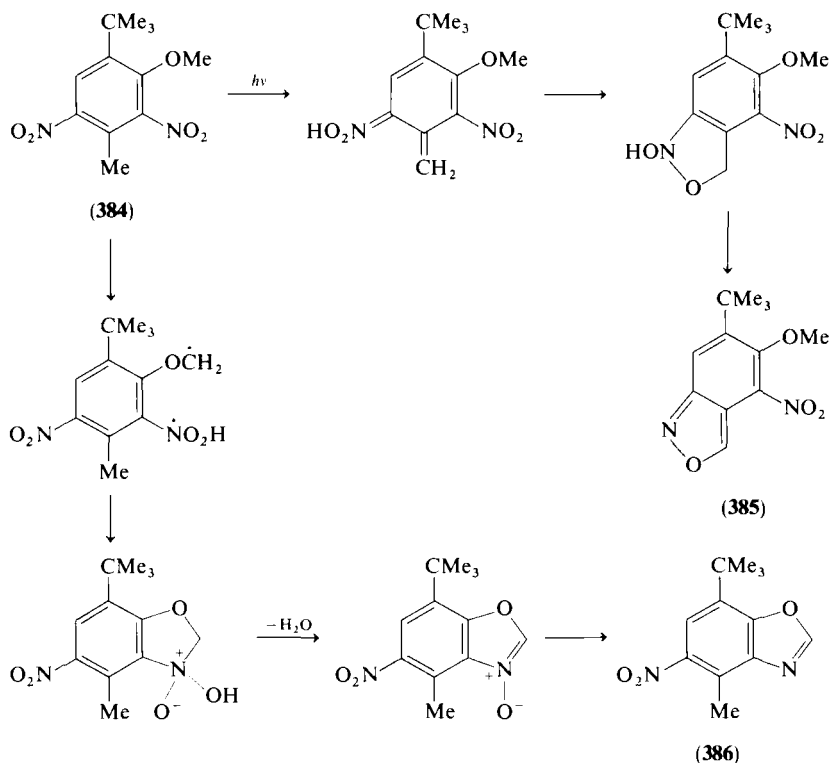
³¹³ Y. Ban, M. Kimura, and T. Oishi, *Heterocycles* **2**, 323 (1974); R. Tadayoni, J. Lacrampe, A. Heumann, R. Furstoss, and B. Waegell, *Tetrahedron Lett.*, 735 (1975); A. M. Farid, J. McKenna, and J. M. McKenna, *J. Chem. Soc. Pak.* **1**, 131 (1979).

³¹⁴ M. E. Kuehne and D. A. Horne, *J. Org. Chem.* **40**, 1287 (1975).

be effected in this way.³¹⁵ Aminyl radicals are similarly generated by photolysis of *N*-nitrosoamines and can be used as shown, for example, in the synthesis of the oxime **380**.³¹⁶

2-Isocyanobiphenyl (**381**) is converted on irradiation in cyclohexane into the cyclohept[*b*]indole **382**³¹⁷; the intramolecular adduct **383** has, without any supporting evidence, been proposed as an intermediate.

Nitro compounds have also been reported to undergo photocyclizations. The intermediacy of an isoxazoline in the photorearrangement of *o*-nitrobenzaldehyde to *o*-nitrosobenzoic acid is now in doubt,³¹⁸ but intramolecular hydrogen abstraction by an excited nitro group in nitrobenzene derivatives can result in the formation of heterocycles. 4-*tert*-Butyl-3-methoxy-2,6-dinitrotoluene (**384**) on irradiation in methanolic sodium hydroxide solution



SCHEME 11

³¹⁵ J.-L. Stein, L. Stella, and H.-M. Surzur, *Tetrahedron Lett.*, 287 (1980).

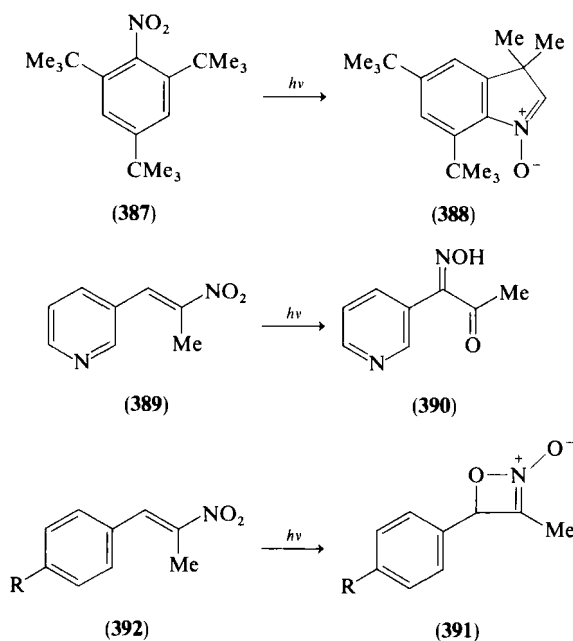
³¹⁶ R. W. Lockhart, M. Kitadani, F. W. B. Einstein, and Y. L. Chow, *Can. J. Chem.* **56**, 2897 (1978).

³¹⁷ J. de Jong and J. H. Boyer, *J. Org. Chem.* **37**, 3571 (1972).

³¹⁸ M. V. George and J. C. Scaiano, *J. Phys. Chem.* **84**, 492 (1980).

is converted in this way to the isoxazole **385** and the oxazole **386**. The proposed pathway is outlined in Scheme 11.³¹⁹ 1-*tert*-Butyl-2-nitrobenzene derivatives undergo related hydrogen abstraction processes to give 1-hydroxy-2-indolinones.³²⁰ The corresponding indolenine N-oxides may be intermediates in these transformations, and indeed 1,3,5-tri-*tert*-butyl-2-nitrobenzene (**387**) is converted on irradiation to the isolable N-oxide **388**.³²¹ *N,N*-Dibenzyl-*o*-nitroanilines undergo photocyclization in methanol in the presence of acid to give benzimidazoles and benzimidazole N-oxides.³²²

Certain α,β -unsaturated nitro compounds are known to undergo photo-rearrangement to ketooximes as illustrated by the conversion of 1-(3-pyridyl)-



2-nitropropene (**389**) into the oxime **390**.³²³ A competing pathway, believed to proceed via initial photocyclization to the unstable oxazete **391**, has recently been reported in substituted nitroalkenes (**392**).³²⁴ A photocycliza-

³¹⁹ D. Döpp, U. Arfsten-Romberg, W. Botz, W. van Hoof, and H. Kosfeld, *Chem. Ber.* **112**, 3946 (1979).

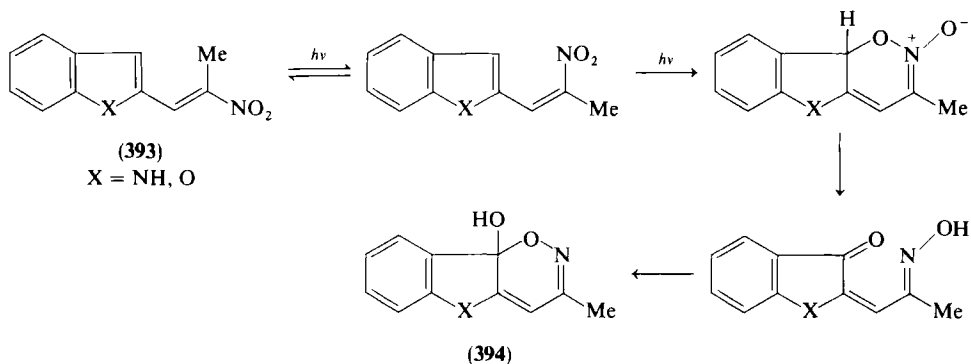
³²⁰ D. Döpp and E. Brugger, *Justus Liebigs Ann. Chem.*, 554 (1979); D. Döpp and K.-H. Sailer, *Chem. Ber.* **108**, 3483 (1975).

³²¹ D. Döpp and K.-H. Sailer, *Chem. Ber.* **108**, 301 (1975).

³²² R. Fielden, O. Meth-Cohn, and H. Suschitzky, *J. C. S. Perkin I*, 696, 705 (1973).

³²³ R. G. Hunt and S. T. Reid, *J. C. S. Perkin I*, 2462 (1977).

³²⁴ I. Saito, M. Takami, and T. Matsuura, *Tetrahedron Lett.*, 3155 (1975).



SCHEME 12

tion of a different type has been observed in nitroalkenes (393) to give 6-hydroxy-1,2-oxazines (394); the pathway shown in Scheme 12 has been proposed.³²⁵ An unprecedented photocyclization has been reported in a 2-nitrobenzylidenehydrazide³²⁶ whereas reductive photocyclization is preferred in 5-nitro-6-styryluracils leading to the formation of 1,3-dimethyl-6-phenylpyrrolo[3,2-*d*]pyrimidines.³²⁷

V. Photoelimination

A. PHOTOELIMINATION OF NITROGEN

The photoelimination of nitrogen from azocycloalkanes is of interest both from the synthetic and mechanistic point of view. Acyclic azoalkanes appear to undergo elimination of nitrogen by a stepwise process involving an intermediate diazenyl radical, but the photoreactions observed in azocycloalkanes are to some extent dependent on ring size.

Photoelimination of nitrogen from diazirines, for example, proceeds via carbene intermediates. 3-*tert*-Butyldiazirine (395) is converted into the cyclopropane 396 and the alkene 397 with the formation of the carbene insertion product being favored from the singlet state.³²⁸ 3-Cyclopropyl-3-chlorodiazirine (398) has similarly been converted to the carbene 399 which undergoes both rearrangement to 1-chlorocyclobutene (400)³²⁹ and addition

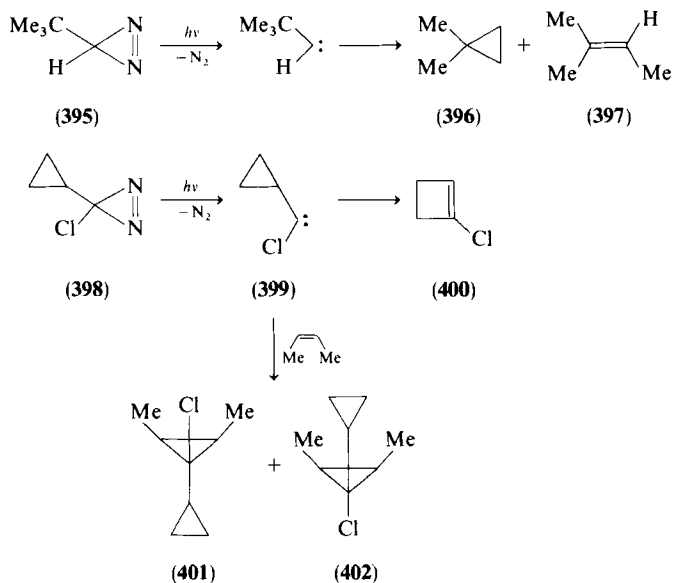
³²⁵ R. Hunt, S. T. Reid, and K. T. Taylor, *Tetrahedron Lett.*, 2861 (1972).

³²⁶ N. E. Alexandrou and J. Stephanidou-Stephanatou, *Chem. Chron.*, 6, 357 (1977).

³²⁷ S. Senda, K. Hirota, M. Suzuki, and M. Takahashi, *Chem. Pharm. Bull.*, 25, 563 (1977).

³²⁸ K.-T. Chang and H. Shechter, *J. Am. Chem. Soc.*, 101, 5082 (1979).

³²⁹ R. A. Moss and M. E. Fantina, *J. Am. Chem. Soc.*, 100, 6788 (1978).



to *cis*-but-2-ene to give the *syn*-chloro- and *anti*-chlorocyclopropanes **401** and **402**.³³⁰ A variety of other carbenes have been generated in this way and intercepted with alkenes.³³¹

Photoelimination of nitrogen from 3,3,4,4-tetramethyldiazetidine has been shown to proceed with a quantum efficiency of 0.52,³³² but no systematic study of the photodecomposition of such compounds has been undertaken. The fused diazine **403** is converted on irradiation into norbornadiene (**404**).³³³

The photoelimination of nitrogen from 1-pyrazolines is one of the most thoroughly investigated photoreactions and it has been used extensively in the synthesis of cyclopropane derivatives.³³⁴ Both stereospecific and non-stereospecific processes have been observed and these are believed, at least in simple 1-pyrazolines, to correspond to singlet and triplet excited states, respectively. Two reaction pathways have been proposed in the azoalkane **405**³³⁵; direct excitation via a thermally activated S_1 state affords the C_6H_6 isomers **406** to **409**, whereas triplet-sensitized excitation results in a tem-

³³⁰ R. A. Moss and R. C. Munjal, *Tetrahedron Lett.*, 2037 (1980).

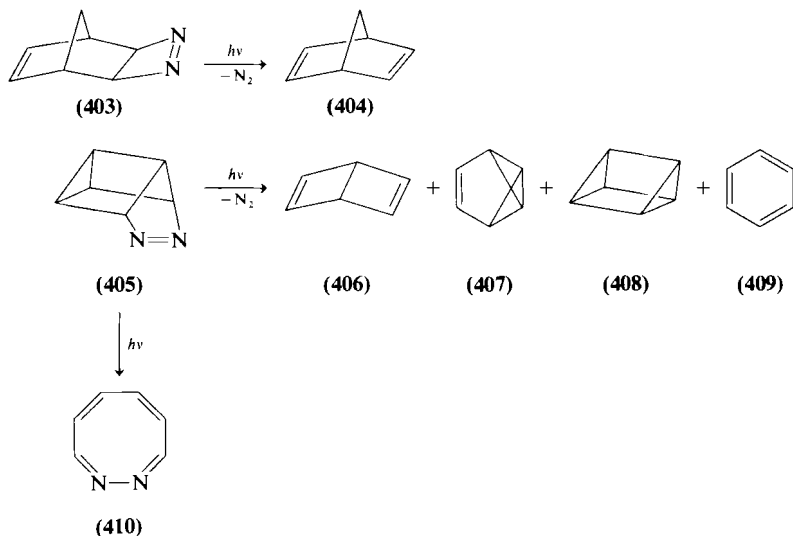
³³¹ R. A. Moss and R. C. Munjal, *J. C. S. Chem. Commun.*, 775 (1978); R. A. Moss, M. E. Fantina, and R. C. Munjal, *Tetrahedron Lett.*, 1277 (1979).

³³² P. S. Engel, R. A. Hayes, L. Keifer, S. Szilagyi, and J. W. Timberlake, *J. Am. Chem. Soc.* **100**, 1876 (1978).

³³³ N. J. Turro, W. R. Cherry, M. F. Mirbach, and M. J. Mirbach, *J. Am. Chem. Soc.* **99**, 7388 (1977).

³³⁴ H. Meier and K.-P. Zeller, *Angew. Chem., Int. Ed. Engl.* **16**, 835 (1977).

³³⁵ N. J. Turro and V. Ramamurthy, *Recl. Trav. Chim. Pays-Bas* **98**, 173 (1979).



perature and solvent independent rearrangement to the 1,2-diazacyclo-octatetraene **410**. Over 95% retention of configuration has been observed in the photoelimination of nitrogen from the 1-pyrazoline **411**.³³⁶ The triplet biradical derived by benzophenone-sensitized irradiation of pyrazoline **412** has been trapped as the peroxide **413** by reaction with oxygen.³³⁷ Direct irradiation affords bicyclo[2.1.0]pentane via the excited singlet state.

Photoelimination of nitrogen from 1-pyrazolines has also been employed in the synthesis of tricyclo[3.2.1.0^{2,4}]oct-6-ene,³³⁸ prismane,³³⁹ quadricyclane,³⁴⁰ "snoutene",³⁴¹ and marasmic acid.³⁴² The trimethylenemethanes **414** have been prepared by photolysis of azoalkanes **415** and characterized spectroscopically.³⁴³ Dimerization and cycloaddition to alkenes of these biradicals have been reported.³⁴⁴

³³⁶ R. L. Dreibelbis, H. N. Khatri, and H. M. Walborsky, *J. Org. Chem.* **40**, 2075 (1975).

³³⁷ R. M. Wilson and F. Geiser, *J. Am. Chem. Soc.* **100**, 2225 (1978).

³³⁸ C. Dietrich-Buchecker, D. Martina, and M. Franck-Neumann, *J. Chem. Res., Synop.*, 78 (1978).

³³⁹ T. J. Katz and N. Acton, *J. Am. Chem. Soc.* **95**, 2738 (1973).

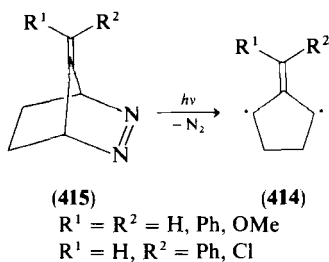
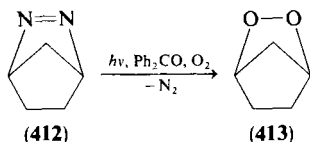
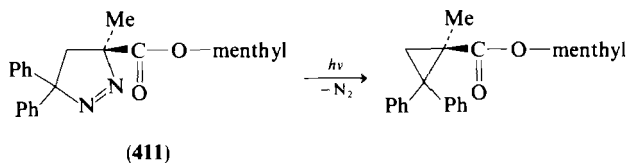
³⁴⁰ N. J. Turro, W. R. Cherry, M. F. Mirbach, and M. J. Mirbach, *J. Am. Chem. Soc.* **99**, 7388 (1977).

³⁴¹ I. Erden and A. de Meijere, *Tetrahedron Lett.*, 1837 (1980).

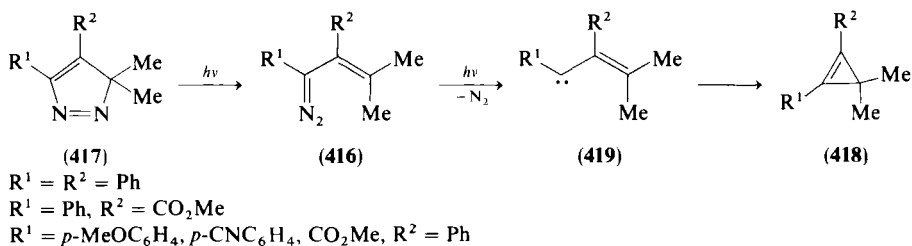
³⁴² W. J. Greenlee and R. B. Woodward, *J. Am. Chem. Soc.* **98**, 6075 (1976).

³⁴³ M. S. Platz, J. M. McBride, R. D. Little, J. J. Harrison, A. Shaw, S. E. Potter, and J. A. Berson, *J. Am. Chem. Soc.* **98**, 5725 (1976); N. J. Turro, M. J. Mirbach, N. Harrit, J. A. Berson, and M. S. Platz, *ibid.* **100**, 7653 (1978).

³⁴⁴ M. S. Platz and J. A. Berson, *J. Am. Chem. Soc.* **98**, 6743 (1976); R. Siemionko, A. Shaw, G. O'Connell, R. D. Little, B. K. Carpenter, L. Shen, and J. A. Berson, *Tetrahedron Lett.*, 3529 (1978).



3*H*-Pyrazoles readily undergo photochemically induced elimination of nitrogen to yield the corresponding cyclopropenes, often by way of detectable vinyl diazo intermediates. 1-Aryl-3-methyl-2-phenyl-1-diazobut-2-enes have, in fact, been prepared in this way from the appropriate pyrazoles.³⁴⁵ The vinyl diazo compounds **416**, obtained by irradiation of the 3*H*-pyrazoles **417**, were further converted to cyclopropenes **418** via vinylmethylene intermediates **419** by irradiation at 10°C.³⁴⁶ 1-Acylcyclopropenes have been



obtained in good yield by photodecomposition of 4-acyl-3*H*-pyrazoles, whereas the ketocarbenes derived from 4-acyl-3*H*-pyrazoles undergo Wolff rearrangement to the corresponding ketenes.³⁴⁷

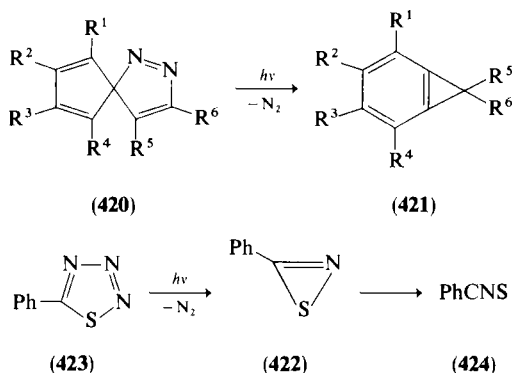
³⁴⁵ J. A. Pincock and K. P. Murray, *Can. J. Chem.* **57**, 1403 (1979).

³⁴⁶ D. R. Arnold, R. W. Humphreys, W. J. Leigh, and G. E. Palmer, *J. Am. Chem. Soc.* **98**, 6225 (1976).

³⁴⁷ M. Franck-Neumann and C. Buchecker, *Tetrahedron Lett.*, 2875 (1973).

Numerous reports of the photoelimination of nitrogen from spiro-3*H*-pyrazoles have been published.³⁴⁸ The diaza[2,2]spirenes **420** were converted into the benzocyclopropenes **421** by a pathway which has been shown not to involve intermediate indazoles.³⁴⁹ 3*H*-Indazoles undergo analogous photoreactions.³⁵⁰

Evidence for the formation of thiiren by photoelimination of nitrogen from 1,2,3-thiadiazoles has been described,³⁵¹ and several thiirens, prepared in this way, have been identified in an argon matrix at 8K.³⁵² Phenylthiazirine (**422**) appears to be an intermediate in the related transformation of 5-phenyl-1,2,3,4-thiatriazole (**423**) into benzonitrile sulfide (**424**),³⁵³ and further



evidence for initial formation of benzothiiren on irradiation of benzothiadiazole has been published.³⁵⁴

Photoelimination of nitrogen from 1,2,3-triazolines has been widely used as a synthetic route to aziridines; the reaction has been reviewed.³⁵⁵ Recent applications include the formation of a new valence isomer (**425**) of azepine from the triazoline **426**,³⁵⁶ and conversion of the triazoline **427** into the aziridine **428**, a process with potential as a synthetic route to mitomycins.³⁵⁷

³⁴⁸ H. Dürr, S. Fröhlich, B. Schley, and H. Weisgerber, *J. C. S. Chem. Commun.*, 843 (1977); H. Dürr and H. Schmitz, *Angew. Chem., Int. Ed. Engl.* **14**, 647 (1975); H. Dürr, W. Schmidt, and R. Sergio, *Justus Liebigs Ann. Chem.*, 1132 (1974).

³⁴⁹ E. Lüddecke, H. Rau, H. Dürr, and H. Schmitz, *Tetrahedron* **33**, 2677 (1977).

³⁵⁰ H. Dürr and A. Hackenberger, *Synthesis*, 594 (1978).

³⁵¹ J. Font, M. Torres, H. E. Gunning, and O. P. Strausz, *J. Org. Chem.* **43**, 2487 (1978).

³⁵² M. Torres, A. Clement, J. E. Bertie, H. E. Gunning, and O. P. Strausz, *J. Org. Chem.* **43**, 2490 (1978); A. Kranz and J. Laurenzi, *J. Am. Chem. Soc.* **99**, 4842 (1977).

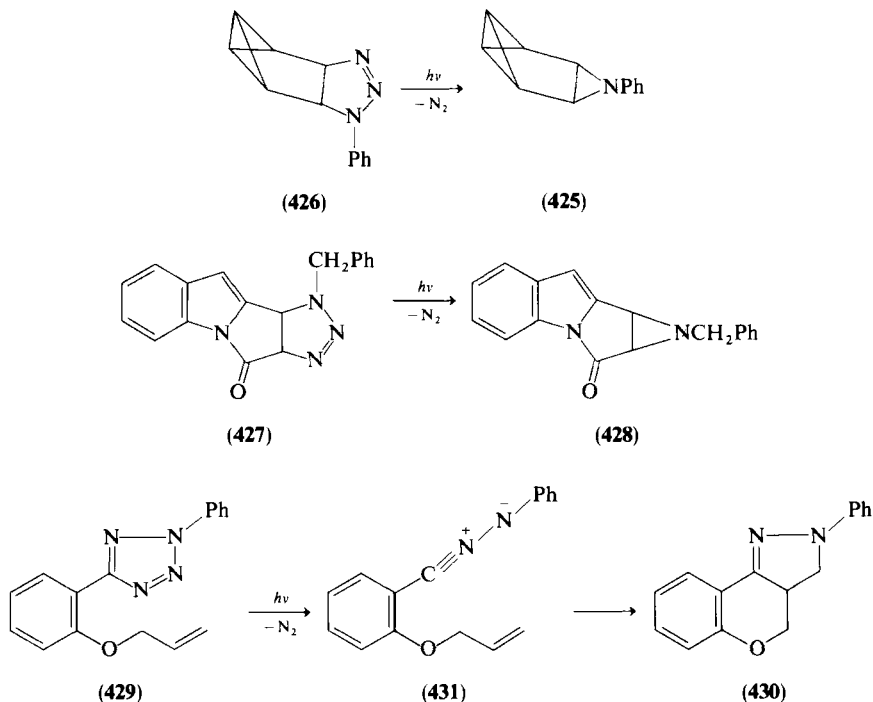
³⁵³ A. Holm, N. Harrit, and I. Trøjberg, *J. C. S. Perkin I*, 746 (1978).

³⁵⁴ R. C. White, J. Scoby, and T. D. Roberts, *Tetrahedron Lett.*, 2785 (1979).

³⁵⁵ J. Burgois, M. Bourgois, and F. Texier, *Bull. Soc. Chim. Fr.*, 485 (1978).

³⁵⁶ M. Christl and H. Leininger, *Tetrahedron Lett.*, 1553 (1979).

³⁵⁷ G. J. Siuta, R. W. Franck, and R. J. Kempton, *J. Org. Chem.* **39**, 3739 (1974).



Photoelimination of nitrogen from the tetrazole **429** results in the formation of the dihydropyrazole **430**, presumably via intramolecular addition of the photochemically generated nitrile imine **431**.³⁵⁸ Other examples of this type of behavior have been reported.³⁵⁹

The photodecomposition of six-membered cyclic azoalkanes has been less systematically investigated although many examples of ring contraction to cyclobutane derivatives have nevertheless been reported.³⁶⁰ The pterodactylane **432**, for example, has been obtained by low-temperature irradiation of the azoalkane **433**.³⁶¹ Photoelimination of nitrogen from 4-*tert*-butylbenzotriazine (**434**) gave the dimer **435** of 2-*tert*-butylbenzazete **436** in low yield,³⁶² and the successful isolation of the *N*-aminoazetidinone **437** from 3-aminonaphthotriazinone (**438**) by irradiation in acetonitrile has been

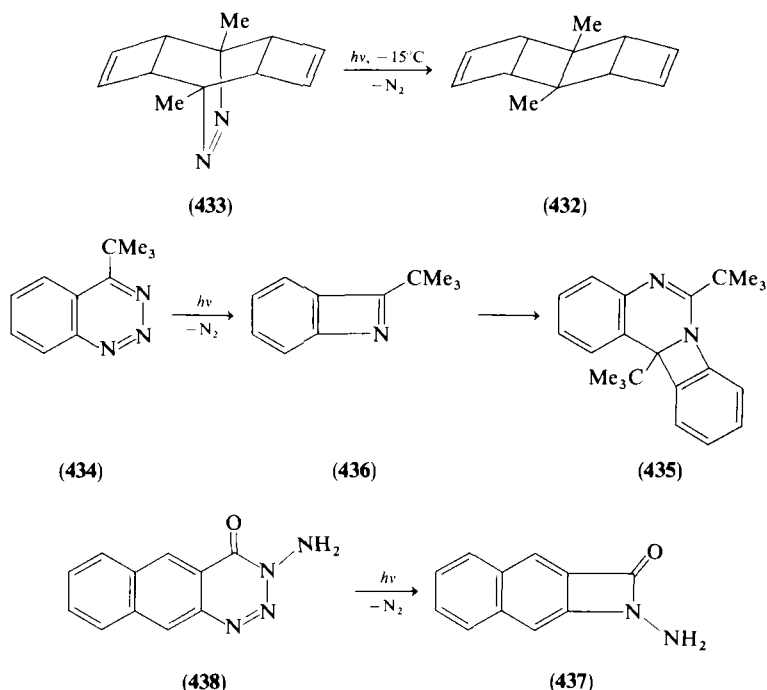
³⁵⁸ H. Meier and H. Heimgartner, *Helv. Chim. Acta* **60**, 3035 (1977).

³⁵⁹ A. Padwa, S. Nahm, and E. Sato, *J. Org. Chem.* **43**, 1664 (1978).

³⁶⁰ N. J. Turro, J. M. Liu, H.-D. Martin, and M. Kunze, *Tetrahedron Lett.*, 1299 (1980); D. Kaufmann and A. de Meijere, *ibid.*, 779 (1979); T. J. Levek and E. F. Kiefer, *J. Am. Chem. Soc.* **98**, 1875 (1976); C. R. Flynn and J. Michl, *ibid.* **96**, 3280 (1974).

³⁶¹ H.-D. Martin and M. Hekman, *Tetrahedron Lett.*, 1183 (1978).

³⁶² C. W. Rees, R. C. Storr, and P. J. Whittle, *Tetrahedron Lett.*, 4647 (1976).



reported.³⁶³ The photolysis of nitrogen from seven-membered and higher cyclic azoalkanes has been little investigated.³⁶⁴

The photoelimination of nitrogen from diazo compounds provides a simple and versatile route for the generation of carbenes, and in certain instances, insertion reactions of carbenes can be employed in the synthesis of heterocycles. Carbenes are believed to be involved at least in part in the photochemically induced conversion of *N,N*-diethyldiazoacetamide (439) into the γ -lactam 440 and the β -lactam 441,³⁶⁵ and a similar approach has been successfully employed in the synthesis of a carbapen-2-em³⁶⁶ and of 7-methylcephalosporin analogues.³⁶⁷ Carbene insertion of a different type has been observed on irradiation of the 6-anilino-5-diazouracils 442 to give the indolo[2,3-*d*]pyrimidines 443.³⁶⁸ Ring contractions in heterocycles

³⁶³ N. Bashir and T. L. Gilchrist, *J. C. S. Perkin I*, 868 (1973).

³⁶⁴ M. Gisin and J. Wirz, *Helv. Chim. Acta* **59**, 2273 (1976); R. M. Pagni, M. N. Burnett, and J. R. Dodd, *J. Am. Chem. Soc.* **99**, 1972 (1977); S. F. Gait, M. E. Peck, C. W. Rees, and R. C. Storr, *J. C. S. Perkin I*, 1248 (1974).

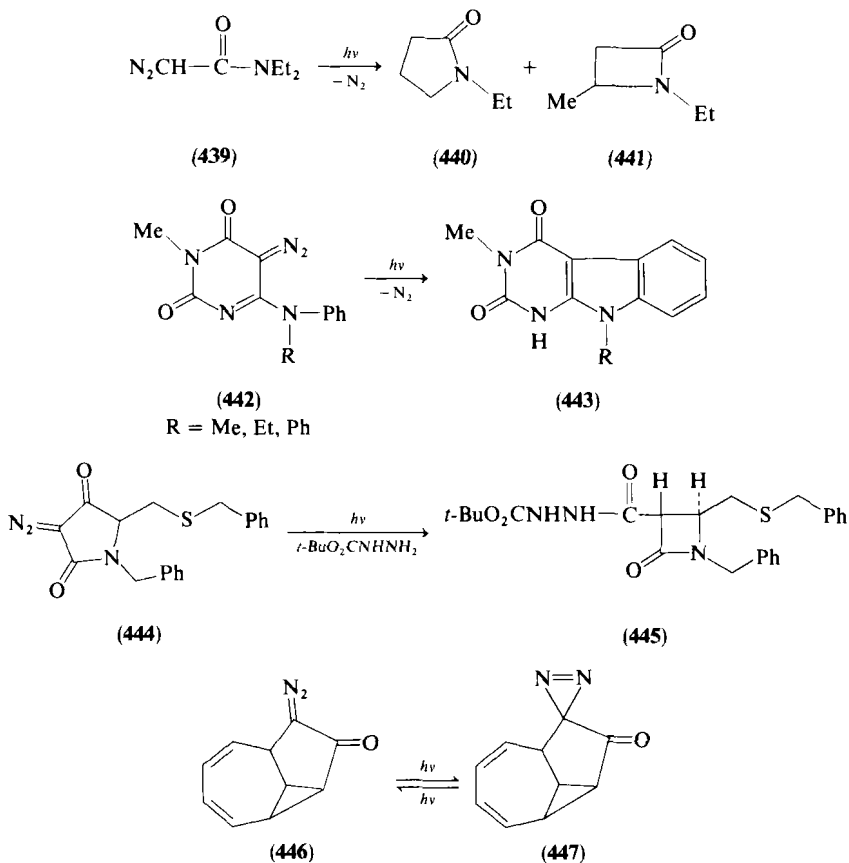
³⁶⁵ H. Tomioka, H. Kitagawa, and Y. Izawa, *J. Org. Chem.* **44**, 3072 (1979).

³⁶⁶ R. W. Ratcliffe, T. N. Salzmänn, and B. G. Christensen, *Tetrahedron Lett.*, 31 (1980).

³⁶⁷ D. M. Brunwin and G. Lowe, *J. C. S. Perkin I*, 1321 (1973).

³⁶⁸ Y. Sakuma and F. Yoneda, *Heterocycles* **6**, 1911 (1977).

arising via α -oxocarbenes have also been reported; photodecomposition of the 3-diazopyrrolidine-2,4-dione **444** in the presence of *tert*-butylcarbazate yields the *cis*- and *trans*- β -lactams **445**.³⁶⁹ Surprisingly, the diazoketone **446** has been shown to undergo a reversible photochemically induced valence isomerization to the diazirene **447**.³⁷⁰



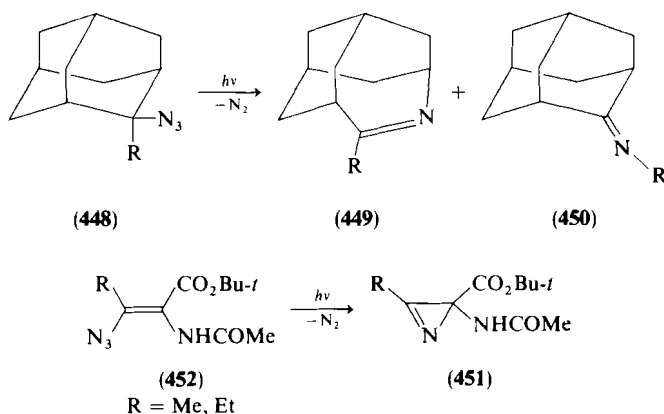
Photoelimination of nitrogen from azides readily affords nitrenes as reactive intermediates. These species undergo a wide variety of transformations involving rearrangement, insertion, and addition, all of which have been used in the synthesis of nitrogen containing heterocycles. Competing 1,2-migrations in nitrenes have been observed on irradiation of 2-azidoadamantanes (**448**) in cyclohexane to give the 4-azahomoadamant-4-enes **449**

³⁶⁹ J. E. T. Corrie, J. R. Hlubucek, and G. Lowe, *J. C. S. Perkin I*, 1421 (1977).

³⁷⁰ T. Miyashi, T. Nakajo, and T. Mukai, *J. C. S. Chem. Commun.*, 442 (1978).

and the imines **450**.³⁷¹ Other systems synthesized in this way include azepine derivatives,³⁷² aza[14]annulene,³⁷³ and aza[18]annulene.³⁷⁴

Further examples of the phototransformation of vinyl azides into 2*H*-azirines, presumably via nitrene intermediates, have been reported.³⁷⁵ The *N*-acetylaminoazirines **451** have been obtained in this way from the azides **452**.³⁷⁶ Fused 2*H*-azirines have long been proposed as intermediates in the photoreactions of aryl and heteroaryl azides, a topic which has recently been the subject of a thorough review.³⁷⁷ Evidence for the intermediacy of 2*H*-azirines comes from successful trapping experiments with suitable nucleophiles. A recent illustration of this type of behavior is the conversion of 9-acetyl-7-azidohexahydrocarbazole (**453**) into the indoloazepines **454** on irradiation in secondary amines.³⁷⁸ The first example of a similar ring expansion in 6-azido-1,3-dimethylthymine (**455**) to give the 1,3,5-triazepine **456** has been described,³⁷⁹ and the synthesis of 3-substituted 2-methoxy-3*H*-azepines has been achieved using methanol as the nucleophile.³⁸⁰



³⁷¹ T. Sasaki, S. Eguchi, and N. Toi, *J. Org. Chem.*, **44**, 3711 (1979).

³⁷² J.-P. Le Roux, P.-L. Desbene, and M. Seguin, *Tetrahedron Lett.*, 3141 (1976); A. Pancrazi and Q. Khuong-Huu, *Tetrahedron*, **31**, 2041 (1975).

³⁷³ H. Röttele and G. Schröder, *Angew. Chem., Int. Ed. Engl.*, **19**, 207 (1980).

³⁷⁴ W. Gilb and G. Schröder, *Angew. Chem., Int. Ed. Engl.*, **18**, 312 (1979).

³⁷⁵ J. Ciabattoni and M. Cabell, *J. Am. Chem. Soc.*, **93**, 1482 (1971); I. Isomura, H. Taguchi, T. Tanaka, and H. Taniguchi, *Chem. Lett.*, 401 (1977).

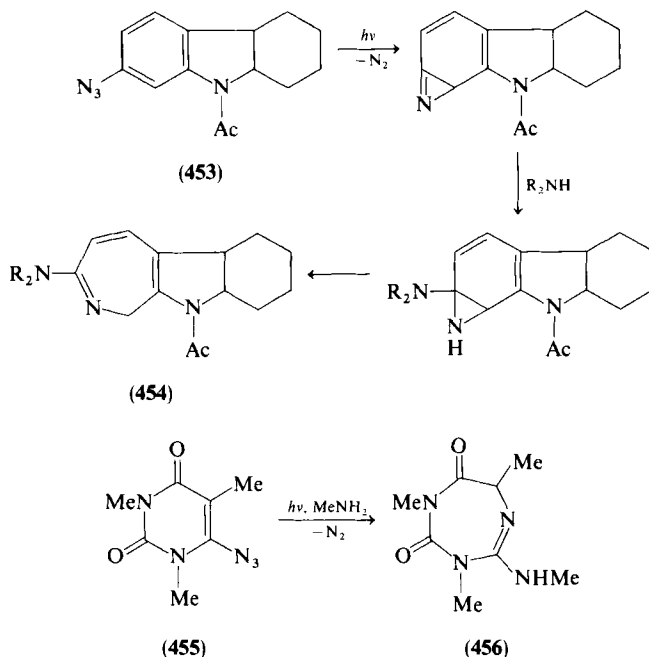
³⁷⁶ C. Shin, K. Watanabe, H. Ohmatsu, and J. Yoshimura, *Tetrahedron Lett.*, 4535 (1978).

³⁷⁷ B. Iddon, O. Meth-Cohn, E. F. V. Scriven, H. Suschitzky, and P. T. Gallagher, *Angew. Chem., Int. Ed. Engl.*, **18**, 900 (1979).

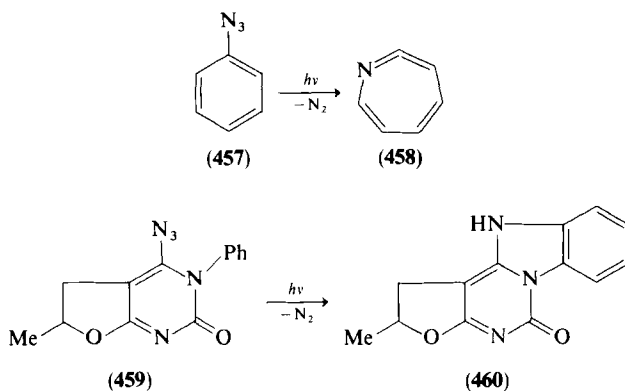
³⁷⁸ E. F. V. Scriven, H. Suschitzky, D. R. Thomas, and R. F. Newton, *J. C. S. Perkin I*, 53 (1979).

³⁷⁹ S. Senda, K. Hirota, T. Asao, K. Maruhashi, and N. Kitamura, *Tetrahedron Lett.*, 1531 (1978).

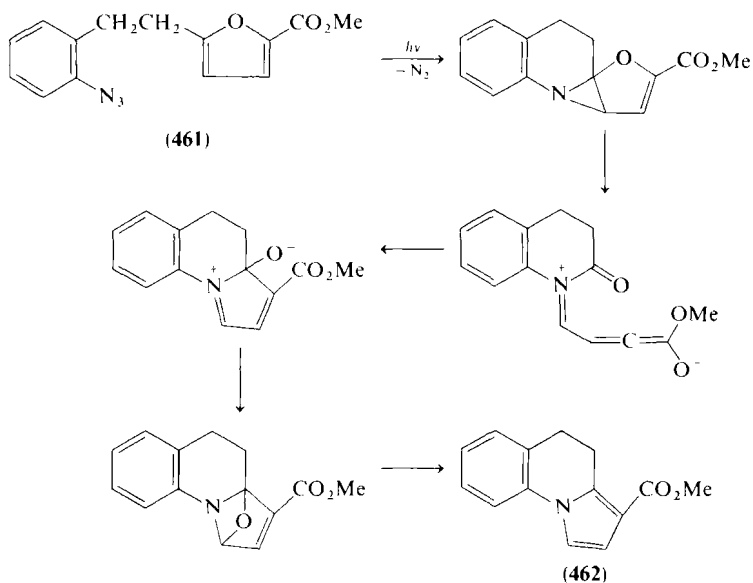
³⁸⁰ R. Purvis, R. K. Smalley, W. A. Strachan, and H. Suschitzky, *J. C. S. Perkin I*, 191 (1978).



An alternative explanation, based on a spectroscopic study involving an argon matrix, has been advanced to account for the singlet photochemistry of phenyl azide (457).³⁸¹ The primary photoproduct is believed to be 1-azacyclohepta-1,2,4,6-tetraene (458). A separate but later study suggests that



³⁸¹ O. L. Chapman and J.-P. Le Roux, *J. Am. Chem. Soc.* **100**, 282 (1978); O. L. Chapman, R. S. Sheridan, and J.-P. Le Roux, *Recl. Trav. Chim. Pays-Bas* **98**, 334 (1979).



SCHEME 13

both types of species are intermediates in the photoelimination of nitrogen from 1-azidonaphthalene.³⁸²

Aryl and heteroaryl nitrene insertion processes have also been employed in the synthesis of heterocycles. The azide **459**, for example, is converted on irradiation into the imidazole **460**,³⁸³ and dihydro-10-thiaisoalloxazines are obtained in good yield on photoelimination of nitrogen from 6-(2-azido-phenylthio)uracils.³⁸⁴

Intermolecular addition of photochemically generated nitrenes and in particular acylnitrenes to alkenes provides a useful and widely applied route to aziridines.³⁸⁵ An analogous intramolecular photoreaction is thought to be involved in the conversion of the *o*-azidophenylethylfuran **461** into the pyrrolo[1,2-*a*]quinoline **462** as outlined in Scheme 13,³⁸⁶ and intramolecular addition to an azo group has been observed in the 8-azido-1-arylaazonaphthalenes **463**.³⁸⁷

³⁸² I. R. Dunkin and P. C. P. Thomson, *J. C. S. Chem. Commun.*, 499 (1980).

³⁸³ H. Wamhoff and C. von Waldow, *Chem. Ber.* **110**, 1730 (1977).

³⁸⁴ T. Hiramitsu and Y. Maki, *J. C. S. Chem. Commun.*, 557 (1977).

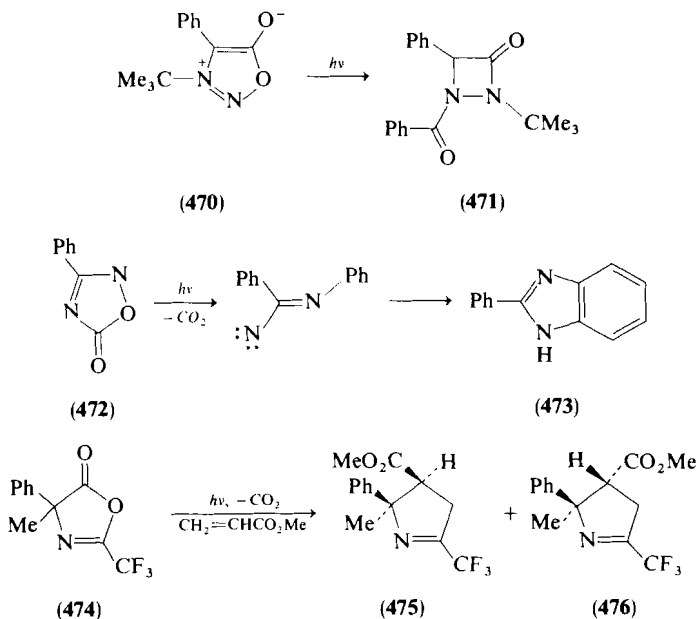
³⁸⁵ T. Kato, Y. Suzuki, and M. Sato, *Chem. Pharm. Bull.* **27**, 1181 (1979); Y. Sato, H. Kojima, and H. Shirai, *J. Org. Chem.* **41**, 3325 (1976); O. E. Edwards, J. W. Elder, M. Lesage, and R. W. Retallack, *Can. J. Chem.* **53**, 1019 (1975).

³⁸⁶ K. Yakushijin, T. Tsuruta, and H. Furukawa, *Heterocycles* **12**, 1021 (1979).

³⁸⁷ P. Spagnolo, A. Tuodo, and P. Zanirato, *J. Org. Chem.* **43**, 2508 (1978).

and with nitriles to give triazoles.³⁹⁰ An intramolecular cycloaddition of a nitrile imine has been observed in the sydnone **468** leading to the formation of the dihydro-3*H*-pyrazolo[2,3-*a*]indole **469**.³⁹¹ Surprisingly, however, 3-*tert*-butyl-4-phenylsydnone (**470**) behaves differently on irradiation to give the diazetidin-3-one **471**,³⁹² and an intermediate azomethine nitrene has been proposed to account for the conversion of oxadiazolin-5-one (**472**) into 2-phenylbenzimidazole (**473**).³⁹³

Photoelimination of carbon dioxide from the 2-oxazolin-5-one **474** in the presence of methyl acrylate affords the *cis*- and *trans*-1-pyrrolines **475** and **476**.³⁹⁴ A nitrile ylid is believed to be involved in this and other analogous transformations.³⁹⁵



³⁹⁰ H. Gotthardt and F. Reiter, *Chem. Ber.* **112**, 1635 (1979).

³⁹¹ H. Meier, H. Heimgartner, and H. Schmid, *Helv. Chim. Acta* **60**, 1087 (1977).

³⁹² Y. Huseya, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jpn.* **45**, 3202 (1972).

³⁹³ J. H. Boyer and P. S. Ellis, *J. C. S. Perkin I*, 483 (1979).

³⁹⁴ M. R. Johnson and L. R. Sousa, *J. Org. Chem.* **42**, 2439 (1977).

³⁹⁵ A. Padwa and S. I. Wetmore, *J. Am. Chem. Soc.* **96**, 2414 (1974).

This Page Intentionally Left Blank

Use of Transition Organometallic Compounds in Heterocyclic Synthesis

BY J. L. DAVIDSON AND P. N. PRESTON

*Department of Chemistry, Heriot-Watt University, Riccarton,
Currie, Edinburgh, United Kingdom*

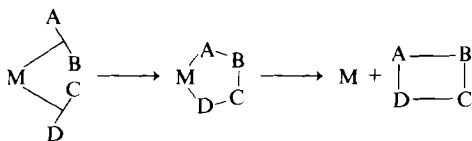
| | |
|--|-----|
| I. Introduction | 321 |
| II. Three-Membered Ring Compounds | 324 |
| A. Vanadium- and Molybdenum-Promoted Epoxidation | 324 |
| B. Synthesis of β -Epoxyketones | 326 |
| III. Four-Membered Ring Compounds | 326 |
| A. Via Organoiron Complexes | 327 |
| B. Via Organopalladium Complexes | 329 |
| C. Via Organocopper Complexes | 330 |
| IV. Five-Membered Ring Compounds | 330 |
| A. With Nitrogen as Heteroatom | 330 |
| 1. Pyrroles | 330 |
| 2. Reduced Pyrroles (Pyrrolidones and Pyrrolidinones) | 334 |
| 3. Indoles | 338 |
| 4. Isoindoles | 343 |
| 5. Carbazoles | 344 |
| B. With Oxygen as Heteroatom | 345 |
| 1. Furans | 345 |
| 2. Reduced Furans | 345 |
| 3. Furan-2-ones (Butenolides and Butyrolactones) | 348 |
| 4. Benzofurans | 351 |
| 5. Isobenzofurans | 354 |
| C. With Sulfur as Heteroatom | 355 |
| 1. Thiophenes | 355 |
| 2. Isobenzothiophenes | 357 |
| D. With Two Heteroatoms (N,N) | 358 |
| 1. Pyrazoles | 358 |
| 2. Indazoles | 360 |
| 3. Cycloheptapyrazoles | 363 |
| 4. Pyrazolodiazepines | 363 |
| 5. Imidazoles | 364 |
| 6. Benzimidazoles | 366 |
| E. With Two Heteroatoms (N,O) | 367 |
| 1. Oxazoles and Benzoxazoles | 367 |
| 2. Isoxazoles | 368 |
| 3. 3a,7b-3-Arylbenzo[3,4]cyclobuta[1,2- <i>d</i>]isoxazoles | 369 |

| | |
|--|-----|
| F. With Two Heteroatoms (N,S) | 370 |
| 1. Thiazoles and Benzothiazoles | 370 |
| 2. Isothiazoles | 370 |
| 3. Condensed Isothiazolium Compounds | 371 |
| G. With Two Heteroatoms (O,S) | 372 |
| Oxathioles | 372 |
| H. With Two Heteroatoms (S,S) | 373 |
| 1. Dithioles | 373 |
| 2. 1,2-Dithiolylum Salts | 374 |
| I. With Three Heteroatoms | 374 |
| 1. Triazoles and Condensed Derivatives | 374 |
| 2. Thiadiazoles | 376 |
| V. Six-Membered Ring Compounds | 376 |
| A. With Nitrogen as Heteroatom | 376 |
| 1. Pyridines | 376 |
| 2. Piperidines | 381 |
| 3. Quinolines | 382 |
| 4. Isoquinolines | 385 |
| B. With Oxygen as Heteroatom | 386 |
| 1. Pyrans | 386 |
| 2. Condensed Pyrans | 388 |
| C. With Sulfur as Heteroatom | 391 |
| Thiapyrans and Thiachromans | 391 |
| D. With Two Heteroatoms (N,N) | 391 |
| 1. Pyrimidines | 391 |
| 2. Pyrazines | 392 |
| 3. Quinazolines and Quinoxalines | 392 |
| 4. Condensed Cinnolines | 393 |
| E. With Two Heteroatoms (N,O) | 394 |
| Oxazines and Benzoxazines | 394 |
| F. With Two Heteroatoms (O,O) | 395 |
| Dioxanes | 395 |
| G. With Three Heteroatoms | 396 |
| <i>s</i> -Triazines | 396 |
| VI. Seven-Membered Ring Compounds | 396 |
| A. With Silicon as Heteroatom | 396 |
| Condensed Silepins | 396 |
| B. With Nitrogen as Heteroatom | 397 |
| Benzazepines | 397 |
| C. With Oxygen as Heteroatom | 397 |
| Condensed Oxepines | 397 |
| D. With Sulfur as Heteroatom | 398 |
| Condensed Thiepinines | 398 |
| E. With Two Heteroatoms (N,N) | 399 |
| Diazepines and Benzodiazepines | 399 |
| F. With Two Heteroatoms (N,O) | 400 |
| Oxazepines | 400 |
| G. With Three Heteroatoms | 401 |
| Oxathiazepines | 401 |
| VII. Macrocycles | 402 |
| 1,2-Diaza-1,5,9-cyclodecatene | 402 |

I. Introduction

The application of organometallic reagents in organic synthesis dates back over 100 years and includes the use of organozinc, -magnesium, -lithium, -boron, -thallium, and -silicon compounds. With the discovery of ferrocene in 1951 the subject of synthetic transition organometallic chemistry expanded rapidly, and many new reagents became available to the preparative organic chemist. A number of texts¹⁻⁵ and a review article⁶ describe the general use of transition organometallic compounds in organic synthesis and this subject is also covered in regular literature surveys.⁷ Applications dealing specifically with the synthesis of heterocyclic compounds are covered up to 1971 in a review by Bird.⁸ We have included some material in that review and updated the coverage to the end of 1979. Reaction products are organized in terms of the type of ring system synthesized and include compounds in which a heterocycle is formed either directly from acyclic substrates or by interconversion of one heterocycle into another. A small number of processes are included in which reactions are effected on intact heterocycles.

Since this review is designed to be of particular use to the synthetic organic chemist it is appropriate to rationalize on a general mechanistic basis the role of the metal in heterocyclic synthesis. In most cases the fundamental processes involved (see Scheme 1) are coordination of the organic substrates to the metal followed by stepwise construction of a linear chain, the ends of



SCHEME 1

¹ C. W. Bird, "Transition Metal Intermediates in Organic Synthesis." Academic Press, New York, 1967.

² J. M. Swan and D. St. C. Black, "Organometallics in Organic Synthesis." Chapman & Hall, London, 1974.

³ J. Tsuji, "Organic Synthesis by Means of Transition Metal Complexes." Springer-Verlag, Berlin and New York, 1975.

⁴ D. Seyferth, ed., "New Applications of Organometallic Reagents in Organic Synthesis." Elsevier, Amsterdam, 1976.

⁵ H. E. Alper, ed., "Transition Metal Organometallics in Organic Synthesis", Vols. 1 and 2. Academic Press, New York, 1976 and 1979.

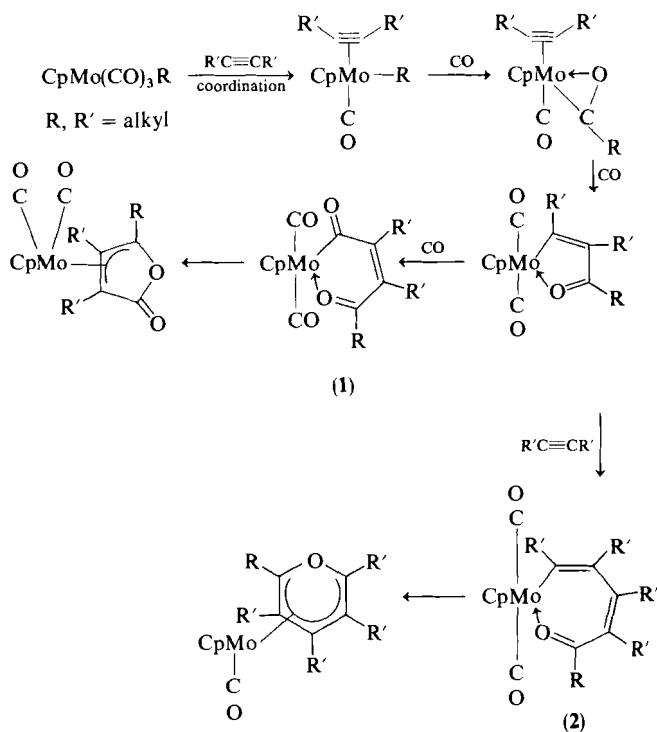
⁶ A. P. Kozikowski and H. F. Wetter, *Synthesis*, 561 (1976).

⁷ See, for example, J. D. Jones, R. Pearce, and R. Whelan, *Annu. Rep.*, **71B**, 243 (1974). L. F. Hedegus, *J. Organomet. Chem.* **163**, 187 (1978).

⁸ C. W. Bird, *J. Organomet. Chem.* **47**, 281 (1973).

which remain attached to the metal. Subsequent ring closure leads to the cyclic product.

The transformations which occur during ring construction involve well documented and established organometallic processes such as orthometallation,⁹ ligand substitution, ligand migration (insertion),¹⁰ oxidative addition, and reductive elimination.¹¹ Stoichiometric organometallic reactions which lead to complexes containing coordinated heterocycles provide us with much useful mechanistic information particularly when reaction intermediates are isolable. This is illustrated by the syntheses of lactone and pyranyl complexes from metal alkyls and acetylenes (Scheme 2). Reactions



SCHEME 2

⁹ M. I. Bruce, *Angew. Chem., Int. Ed. Engl.* **16**, 73 (1977).

¹⁰ (a) J. Falbe, "Synthesen mit Kohlenmonoxid." Springer-Verlag, Berlin and New York, 1967; (b) C. W. Bird, *Chem. Rev.* **62**, 283 (1962); M. Ryang and S. Tsutsumi, *Synthesis*, 55 (1971); (c) L. Cassar, G. P. Chiusoli, and F. Guerrieri, *ibid.*, 509 (1973).

¹¹ R. F. Heck, "Organotransition Metal Chemistry: A Mechanistic Approach." p. 49. Academic Press, New York, 1974.

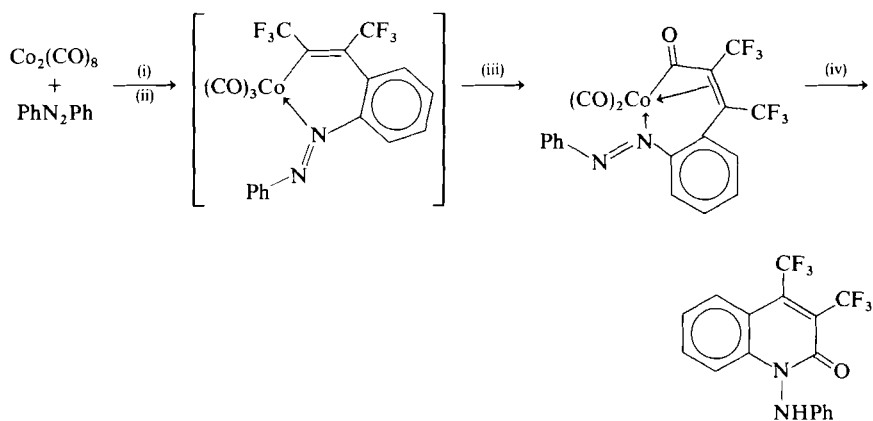
¹² H. G. Alt, *J. Organomet. Chem.* **127**, 349 (1977).

of this type have been shown to proceed via a sequence of CO and acetylene insertions leading to metallocyclic species **1** and **2** which undergo ring closure via internal nucleophilic attack of the oxygen heteroatom on the metallated carbon atom.¹²⁻¹⁴

The latter process appears to be a crucial step in reactions leading to heterocycles. The cyclization is promoted by the metal in two distinct ways: (a) by holding the two atoms of the incipient heterocycle in close proximity, and (b) by activating the coordinated atoms toward nucleophilic or electrophilic attack.

A variety of heterocycles can be synthesized utilizing the propensity of metals to form a metal-carbon bond at the ortho position of a substituted benzene—the orthometallation reaction⁹; an example of this type of process is illustrated in Scheme 3.¹⁵ In this case the CO insertion step probably results from coordination of the $\text{CF}_3\text{C}\equiv\text{CCF}_3$ moiety in contrast with Scheme 2 where coordination of an external species is required. Many metal carbonyl-promoted heterocyclic syntheses lead to ring systems in which the heteroatom lies adjacent to a ketonic CO group. This results because the process immediately preceding ring closure frequently involves a coordination promoted CO insertion.

Finally the ability of metals to undergo oxidative addition and reductive elimination during heterocyclic synthesis is highlighted. This process is of



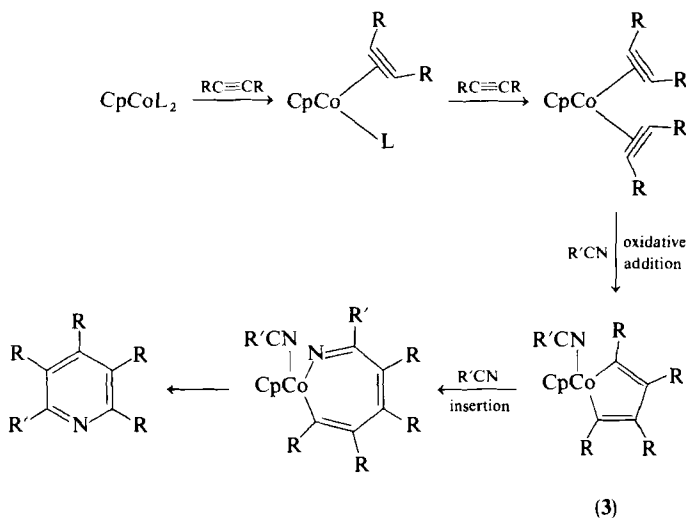
SCHEME 3. (i) Orthometallation; (ii) $\text{CF}_3\text{C}\equiv\text{CCF}_3$ insertion; (iii) CO insertion; (iv) ring closure and N-protonation.

¹³ M. Green, J. Z. Nyathi, C. Scott, F. G. A. Stone, A. J. Welch, and P. Woodward, *J. C. S. Dalton*, 1017 (1978).

¹⁴ M. Bottrill and M. Green, *J. C. S. Dalton* 820 (1979).

¹⁵ M. I. Bruce, B. L. Goodall, and F. G. A. Stone, *J. C. S. Dalton* 1651 (1975).

particular significance in many metal-promoted organic reactions and in the context of heterocyclic synthesis is illustrated by the cobalt-promoted pyridine synthesis in Scheme 4.¹⁶ Coupling of the two acetylenes and a nitrile molecule proceeds via a metallocycle (3) in which the metal has undergone oxidative addition with two acetylenes; subsequent ring expansion involving coordination and insertion of $R'C\equiv N$ produces a metallocycle which on reductive elimination yields the pyridine derivative.



SCHEME 4

II. Three-Membered Ring Compounds

A. VANADIUM- AND MOLYBDENUM-PROMOTED EPOXIDATION

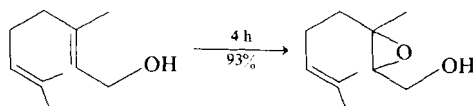
The molybdenum-catalyzed conversion of alkenes into epoxides by alkyl hydroperoxides is an important commercial process.^{17,18} The synthetic potential of such reactions in regard to more complex organic molecules has been evaluated¹⁹; alkyl hydroperoxides are used as oxidants in the

¹⁶ Y. Wakatsuki and H. Yamazaki, *J. C. S. Dalton*, 1278 (1978).

¹⁷ See, for example, the Halcon process for synthesis of propylene oxide: J. Kollar, U.S. Patent 3,360,584 (1967).

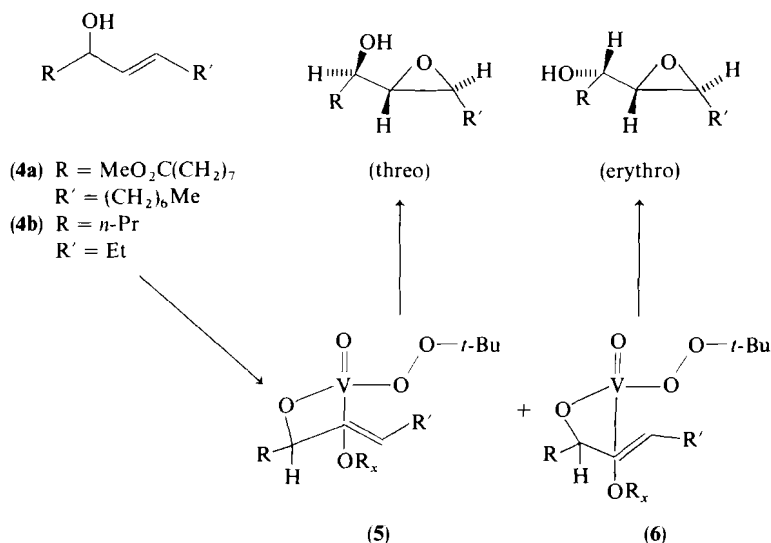
¹⁸ Cf. R. Hiatt, in "Oxidation", (R. L. Augustine, ed.), Vol. 2, Chapter 3. Dekker, New York, 1971.

¹⁹ K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.* **95**, 6136 (1973); for a recent review, see P. A. Bartlett, *Tetrahedron* **36**, 3 (1980).

SCHEME 5. Reagents: $\text{VO}(\text{acac})_2$, $t\text{-BuO}_2\text{H}$, C_6H_6 , 20°C .²⁰

presence of coordination compounds such as $\text{VO}(\text{acac})_2$ or organometallic compounds such as $\text{Mo}(\text{CO})_6$ (Scheme 5). The reaction rates and stereoselectivities observed¹⁹ in epoxidation of cyclohexenols is enhanced compared with analogous reactions using peroxybenzoic acid.²¹

In acyclic secondary *E*-allylic alcohols, epoxidation by the vanadium system shows opposite stereospecificity to that of peracid and molybdenum carbonyl-mediated epoxidation (see Scheme 6)²² The predominance of the erythro isomer in the former process is rationalized²² in terms of the energetically more favorable transition state (**6**, cf. **5**) and in this context the mechanism has analogy in the epoxidation behavior of medium-ring cyclic allylic alcohols.²³



SCHEME 6

²⁰ K. B. Sharpless, R. C. Michaelson, and J. D. Cutting, *J. Am. Chem. Soc.* **96**, 5254 (1974).

²¹ H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

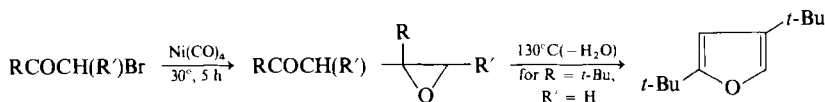
²² (a) E. D. Mihelich, *Tetrahedron Lett.*, 4729 (1979). (b) B. E. Rossiter, T. R. Verhoeven, and K. B. Sharpless, *Tetrahedron Lett.*, 4733 (1979). Paper 22b contains material correcting part of the work described in Ref. 20.

²³ T. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, *J. Am. Chem. Soc.* **101**, 159 (1979).

The vanadium-promoted epoxidation method has proved to be valuable in synthetic routes leading to *dl*-C₁₈ *Cecropia* juvenile hormone²⁰ and lasalocid A.²⁴ The mechanism of vanadium-mediated epoxidation has been elucidated²⁵ but an evaluation of the use of other organometallic compounds as epoxidation reagents is required.²⁶

B. SYNTHESIS OF β -EPOXYKETONES

β -Epoxyketones can be prepared by peracid epoxidation of β,γ -unsaturated ketones²⁷ but easy rearrangement of the latter to α,β -unsaturated ketones can be a problem. Direct synthesis of such epoxides by reaction of α -bromoketones and nickel carbonyl is thus a valuable process (Scheme 7).²⁸ The product epoxides can be converted by thermal reactions into unsymmetrically substituted furans (Scheme 7).²⁸



SCHEME 7

The mechanism of epoxide formation (Scheme 7) has not been established but the intermediacy of nickel enolates and ensuing aldol type reactions are suspected²⁸ (cf. Zn-mediated formation of furans from α -bromoketones²⁹). A limitation on the synthesis is that R cannot be aryl: for these cases, the products are 2,4-diarylfurans (see Section IV,B,1).³⁰

III. Four-Membered Ring Compounds

Four different synthetic methods leading to azetidones and condensed analogs have been described. These are discussed below in relation to the types of organometallic complexes used as reactants or envisaged as intermediates.

²⁴ T. Nakata, G. Schmidt, B. Vranesic, M. Ogikawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.* **100**, 2933 (1978).

²⁵ Cf. A. O. Chong and K. B. Sharpless, *J. Org. Chem.* **42**, 1587 (1977).

²⁶ Cf. J. P. Schirmann and F. R. Weiss, German Patent 2,446,830 (1975) [*CA* **83**, 58637 (1975)] in which the use of W(CO)₆ is described.

²⁷ See, for example, H. Freitel and P. Baranger, *C. R. Acad. Sci.* **241**, 674 (1955).

²⁸ E. Yoshisato and S. Tsutsumi, *J. Am. Chem. Soc.* **90**, 4488 (1968).

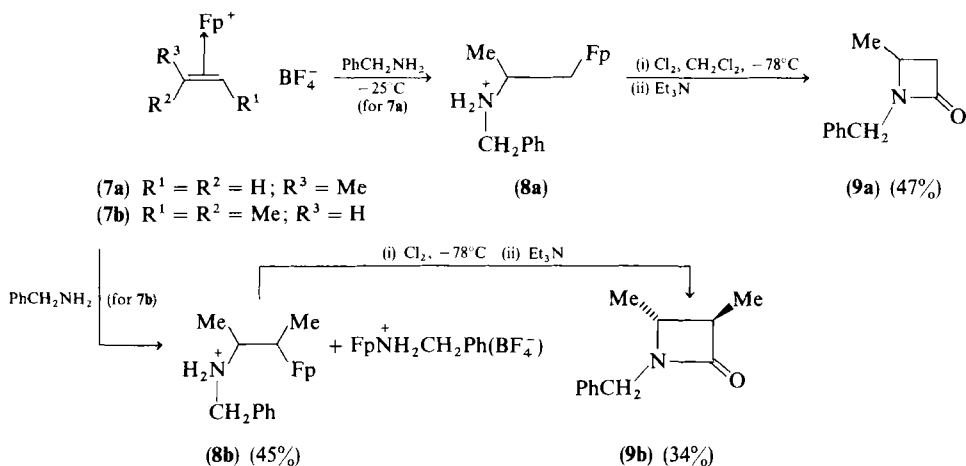
²⁹ T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Am. Chem. Soc.* **89**, 5727 (1967).

³⁰ E. Yoshisato and S. Tsutsumi, *Chem. Commun.*, 33 (1968).

A. VIA ORGANOIRON COMPLEXES³¹

Cationic Fp (olefin) complexes $[\text{Fp} = \eta^5\text{-C}_5\text{H}_5\text{Fe}(\text{CO})_2]$ undergo regio-specific addition of heteroatomic nucleophiles.³² Subsequent ligand transfer (carbonyl insertion) occurs with retention of configuration at the migrating center ($\text{R-Fe-CO} \rightarrow \text{RCOFe}$).³³ A combination of these processes has provided a novel stereospecific azetidinone synthesis which can also be applied to condensed systems.³⁴

Organoiron complexes (7) are converted in high yield into ammonium salts (8); these in turn undergo oxidatively induced ligand transfer and cyclization to give azetidinones (9) in moderate yields (Scheme 9). Formation of the trans product (9b) indicates a stereochemical sequence of trans addition to the olefin complex followed by carboxamidation with retention of configuration at the C—Fe bond.



SCHEME 9

Two variants of this method have been devised in which milder oxidants can be employed. Lead dioxide or silver oxide convert the free base of 8a into the azetidinone in good yield, perhaps³⁴ via intermediate radical cations

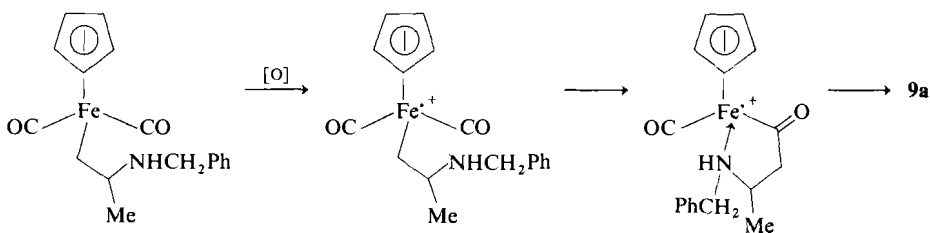
³¹ Cf. M. Rosenblum, *Acc. Chem. Res.* **7**, 122 (1974).

³² P. Lennon, M. Madhavarao, A. Rosan, and M. Rosenblum, *J. Organomet. Chem.* **108**, 93 (1976).

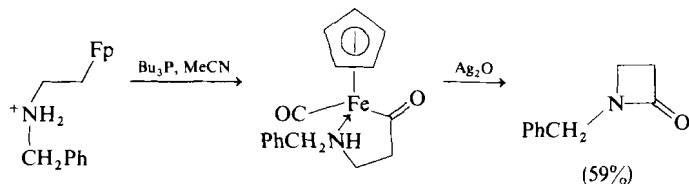
³³ K. M. Nicholas and M. Rosenblum, *J. Am. Chem. Soc.* **95**, 4449 (1973); P. L. Bock, D. J. Boschetto, J. R. Rasmussen, J. P. Deemers, and G. M. Whitesides, *ibid.* **96**, 2814 (1974).

³⁴ P. K. Wong, M. Madhavarao, D. F. Marten, and M. Rosenblum, *J. Am. Chem. Soc.* **99**, 2823 (1977).

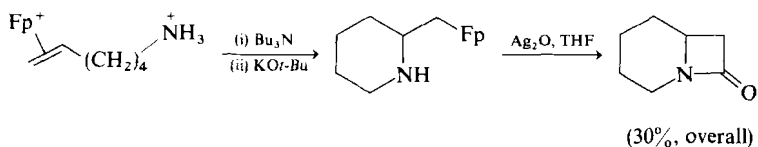
(Scheme 11). Alternatively the quaternary salts can be converted thermally into acyliron chelate complexes which can then be oxidized to azetidinones (Scheme 12). Extension of the method to the synthesis of a condensed azetidinone is illustrated in Scheme 13, but the scope of the procedure has not been evaluated. It will also be of interest to assess the utility of other cationic organometallic complexes: preliminary studies have shown that molybdenum complexes behave in an analogous manner but the oxidative cyclization is inefficient (Scheme 14).



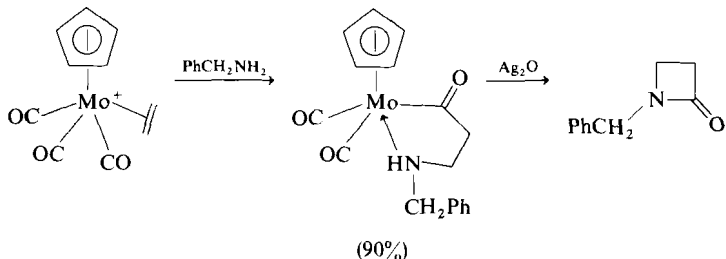
SCHEME 11



SCHEME 12



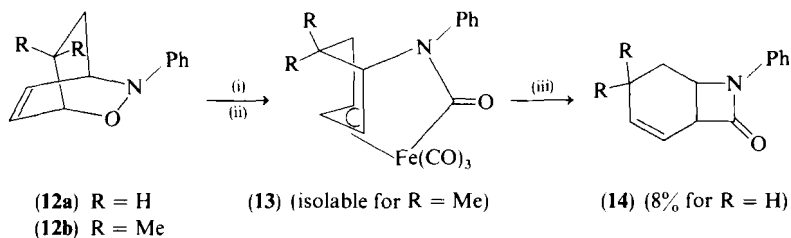
SCHEME 13



SCHEME 14

An elaboration of cyclizations of this type can be anticipated in regard to the reaction of nucleophiles with cationic acetylene complexes³⁵ but such substrates are less extensively characterized.³⁶

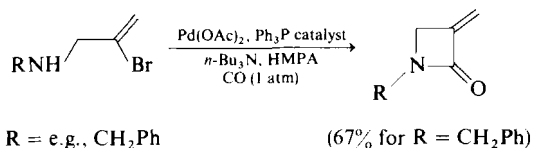
The nonacarbonyldiiron-induced transformation of oxazabicyclo[2.2.2]octenes (**12**) into condensed azetidinones is intriguing mechanistically but will obviously have limited synthetic application (Scheme 15).³⁷ The β -lactam (**14a**), among other products, is isolated directly from the iron carbonyl reaction but the dimethyl analog (**14b**) is obtained by pyrolysis of an isolable intermediate σ - π -allyl complex (**13b**).



SCHEME 15. (i) $\text{Fe}_2(\text{CO})_9$, (ii) CO, (iii) C_6H_6 , 80°C (for **12b**).

B. VIA ORGANOPALLADIUM COMPLEXES

The insertion of carbon monoxide into readily available 2-bromo-3-aminopropene derivatives can be effected by catalytic quantities of palladium acetate and triphenylphosphine; high CO pressures are not required (Scheme 16).³⁸ The β -lactam products presumably arise by palladation, carbonylation, and cyclization as depicted in Scheme 17.³⁸ An extension of this approach to the synthesis of biologically interesting condensed β -lactams can be expected.



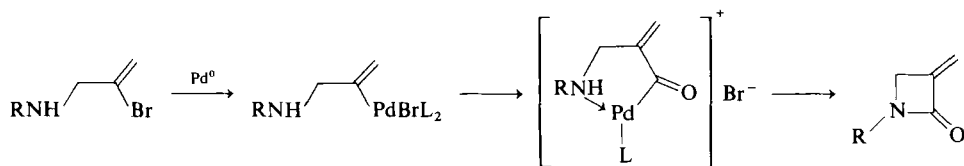
SCHEME 16

³⁵ S. Samuels, S. R. Berryhill, and M. Rosenblum, *J. Organomet. Chem.* **166**, C9 (1979).

³⁶ M. Bottrill and M. Green, *J. C. S. Dalton*, 2365 (1977).

³⁷ Y. Becker, A. Eisenstadt, and Y. Shvo, *Tetrahedron*, 799 (1978).

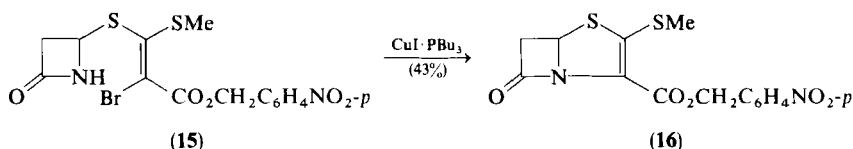
³⁸ M. Mori, K. Chiba, M. Okita, and Y. Ban, *J. C. S. Chem. Commun.*, 698 (1979).



SCHEME 17

C. VIA ORGANOCOPPER COMPLEXES

Z-Bromodithioketene acetal derivatives (**15**) can be transformed into 2-thioalkyl-substituted penems (**16**) by copper(I) halides³⁹ (Scheme 18). The process is especially attractive because of the ready availability of requisite functionalized secolactams (cf. **15**) and also because of the tolerance of a variety of functional groups to the cyclizing agent.



SCHEME 18

The mechanism presumably involves initial oxidative addition of the alkenyl halide to the Cu(I) species and ensuing cyclization; analogy for this type of process is provided by the Cu(I) -mediated reaction of phthalimide anions with alkenyl and aryl halides.⁴⁰ The *E*-isomer of **15** reacts in a different fashion to give an isothiazolidinone derivative, albeit in low yield.

IV. 5-Membered Ring Compounds

A. WITH NITROGEN AS HETEROATOM

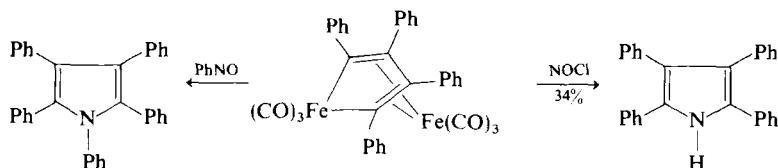
1. Pyrroles

Both iron- and nickel-mediated cyclooligomerization processes have been used in direct routes to pyrrole derivatives. Preformed ferracyclopentadiene complexes can be converted in moderate yields into 2,3,4,5-tetraphenyl-

³⁹ F. DiNinno, E. V. Linek, and B. G. Christensen, *J. Am. Chem. Soc.* **101**, 2210 (1979).

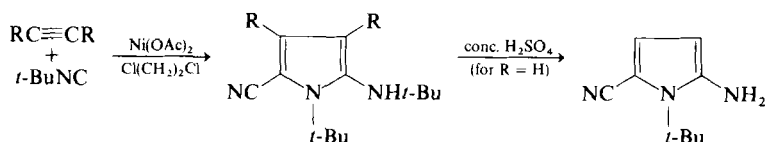
⁴⁰ R. G. R. Bacon and A. Karim, *J. C. S. Perkin I*, 272, 278 (1973).

pyrroles in processes that have analogy in the chemistry of rhoda- and cobaltacyclopentadienes (see Scheme 19 and Sections IV,B,5 and C,1).⁴¹⁻⁴³



SCHEME 19

A more complex reaction is involved in the cooligomerization of acetylenes and *tert*-butyl isocyanide using nickel acetate as the catalyst (Scheme 20)⁴³; the nature of intermediate complexes leading to the formation of 2-cyano-5-*tert*-butylaminopyrroles has not been established. Cocyclization of *tert*-butyl isocyanide with coordinated hexafluoro-2-butyne gives rise to coordinated cyclopentadienone anils for molybdenum systems,⁴⁴ hence the nature of acetylene substituents and of the organometallic catalyst play crucial roles in these processes. The pyrrole products from the former reaction can be decomposed by sulfuric acid and the overall sequence provides a simple synthesis of 5-amino-2-cyanopyrroles (Scheme 20).



SCHEME 20

The discovery⁴⁵ that santonin is converted by enneacarbonyldiiron in a thermal process into products that are akin to those from uncatalyzed photolysis has encouraged further work in this area.

From studies of the reactions of 2-arylazirines it is evident that transition metal carbonyls can also effect reactions under mild conditions to give products that would be obtained from alternative pyrolysis procedures.

⁴¹ E. H. Bray, C. Hoogzand, W. Hübel, U. Krüerke, R. Merenyi, and E. Weiss, *Proc. Int. Conf. Coord. Chem.*, 6th, 1961, 190 (1961).

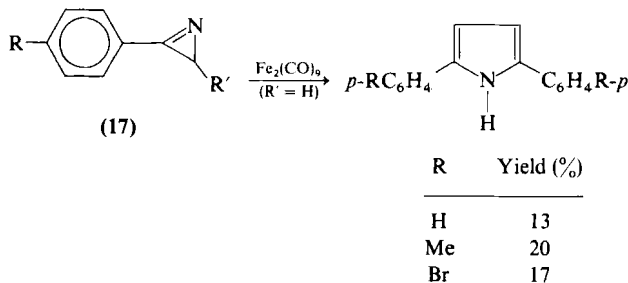
⁴² I. Wender and P. Pino (eds.), "Organic Synthesis Via Metal Carbonyls," p. 330. Wiley (Interscience), New York, 1968.

⁴³ M. Jautelat and K. Ley, *Synthesis*, 593 (1970); German Patent 1,951,965 (1971) [*CA* 75, 35719 (1971)].

⁴⁴ J. L. Davidson, M. Green, J. Z. Nyathi, F. G. A. Stone, and A. J. Welch, *J. C. S. Dalton*, 2246 (1977).

⁴⁵ H. Alper and E. C. H. Keung, *J. Am. Chem. Soc.* 94, 2144 (1972).

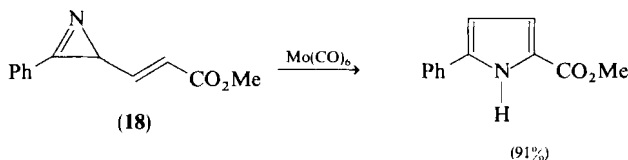
Whereas the reaction of 2-aryl azirines (**17**, $R'=H$, Scheme 21) with group VI metal carbonyls [$M(CO)_6$; $M=Cr, Mo, W$] gives rise to pyrazines (see Section V,C,2)^{46,47} the reaction of enneacarbonyldiiron produces 2,5-diarylpyrroles albeit in poor yield (Scheme 21)⁴⁸; four organoiron complexes can also be isolated. Key steps in the mechanism are thought to include the formation of an azirine complex and ring opening by C—N cleavage to give a coordinated alkenylnitrene-iron carbonyl species.⁴⁸



SCHEME 21

The presence of a 2-substituent in 3-phenylazirines (**17**, $R'=H$ in Scheme 21) modifies the mode of reaction with molybdenum carbonyl.⁴⁷ In contrast to pyrazine formation for (**17**, $R'=H$; see Section V,C,2), the alkenyl azirine (**18**, Scheme 22) is transformed in excellent yield into 2-phenyl-5-carboxymethylpyrrole. This product probably arises by intramolecular cyclization within an intermediate dienylnitrene intermediate, and related reactions have been devised to synthesize isoxazoles (see Section IV,E,2) and pyrazoles (see Section IV,D,1).⁴⁷ The molybdenum carbonyl-promoted formation of 2,5-disubstituted pyrroles⁴⁷ has analogy in uncatalyzed thermal, but not photochemical decomposition of 3-phenyl-2*H*-azirine 2-acrylate.⁴⁹

Pyrroles among other products are also formed from diiron enneacarbonyl or molybdenum carbonyl-induced decomposition of the *Z*-ketovinylazirine



SCHEME 22

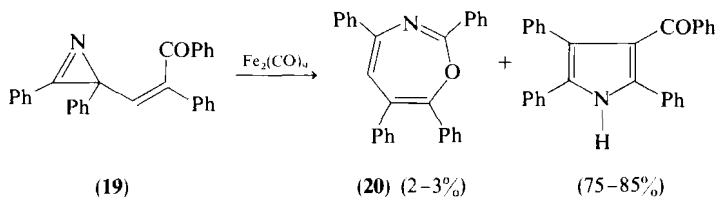
⁴⁶ H. Alper and S. Wollowitz, *J. Am. Chem. Soc.* **97**, 3541 (1975).

⁴⁷ H. Alper, J. E. Prickett, and S. Wollowitz, *J. Am. Chem. Soc.* **99**, 4330 (1977).

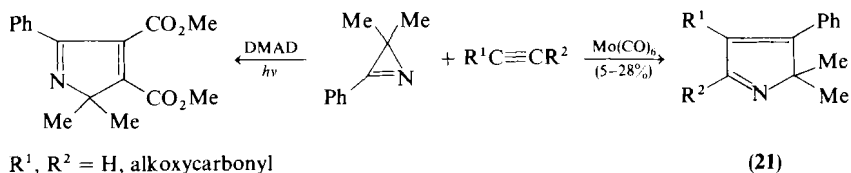
⁴⁸ H. Alper and J. E. Prickett, *J. C. S. Chem. Commun.*, 191 (1976).

⁴⁹ A. Padwa, J. Smolanoff, and A. Tremper, *J. Am. Chem. Soc.* **97**, 4682 (1975).

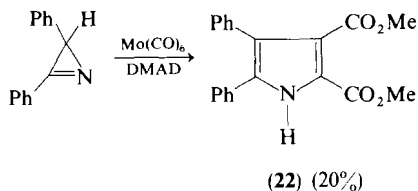
derivative **19** (Scheme 23).^{50,51} In this case the product contrasts markedly with that from both thermal and photochemical decomposition which produce the oxazepin derivative **20** in 90% yield.^{51,52}

SCHEME 23⁵⁰

The formation of 2*H*-pyrroles (**21**) and a pyrrole derivative (**22**) from the reaction of 3-phenyl-2*H*-azirines and acetylenic esters in the presence of molybdenum hexacarbonyl is intriguing mechanistically (Schemes 24, 25).⁵³ Carbon-nitrogen bond cleavage must occur perhaps via a molybdenum complex (cf. **23** in Scheme 26) but intermediate organometallic species have not yet been isolated.⁵³ Despite the relatively poor yields of 2*H*-pyrrole products, the process is synthetically valuable since the equivalent uncatalyzed photochemical process produces isomeric 2*H*-pyrroles from a primary reaction of azirine C—C cleavage⁵⁴ (Scheme 24).



SCHEME 24



SCHEME 25

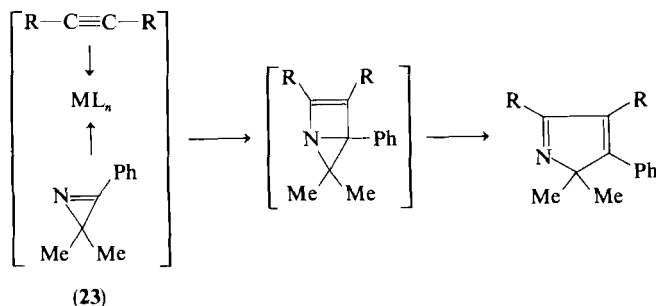
⁵⁰ F. Bellamy, *J. C. S. Chem. Commun.*, 998 (1978).

⁵¹ F. Bellamy, *Tetrahedron Lett.*, 4577 (1978).

⁵² J. P. Le Roux, J. C. Cherton, and P. L. Desbene, *C. R. Acad. Sci.* **280**, 37 (1975).

⁵³ A. Inada, H. Heimgartner, and H. Schmid, *Tetrahedron Lett.*, 2983 (1979).

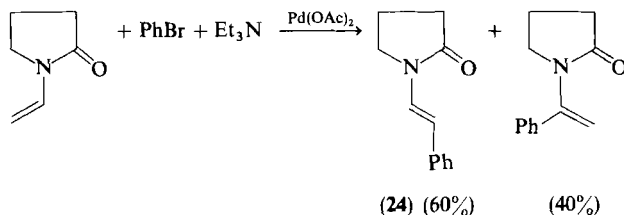
⁵⁴ V. Gerber, H. Heimgartner, H. Schmidt, and W. Heinzelmann, *Helv. Chim. Acta* **60**, 687 (1977).



SCHEME 26

2. Reduced Pyrroles (Pyrrolidones and Pyrrolidinones)

A useful palladium-promoted reaction on an intact pyrrolidone is illustrated in Scheme 27 in which a 1-vinyl derivative is arylated to give both 1- and 2-isomers.⁵⁵ Compounds of type **24** may prove to be useful precursors for the synthesis of pharmacologically valuable 2-arylethylamines. A related palladium-catalyzed process is described in the section on furans. (see Eq. 14 in Section IV,B,1).



SCHEME 27

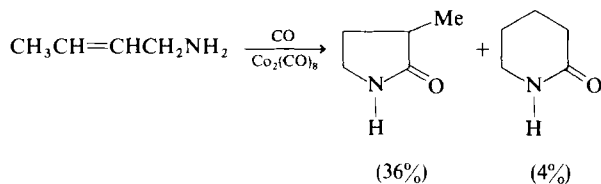
The formation of cyclic amides from suitably substituted aminoalkenes by hydrocarboxylation was first reported by Falbe and his co-workers¹⁰ and has been summarized by Bird⁸; an example illustrating the synthesis of a pyrrolidone⁵⁶ is given in Scheme 28. Both five- and six-membered ring products may be obtained depending on the degree of substitution at the double bond.^{56,57}

A more complex type of carbonylation occurs when cyclopropylamine is treated with carbon monoxide in the presence of catalytic amounts of the

⁵⁵ C. B. Ziegler and R. F. Heck, *J. Org. Chem.* **43**, 2949 (1978).

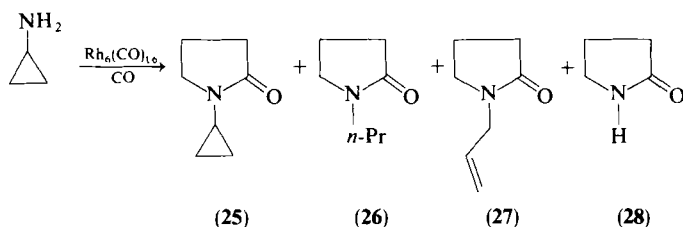
⁵⁶ J. Falbe and F. Korte, *Chem. Ber.* **95**, 2680 (1962).

⁵⁷ J. Falbe and F. Korte, *Chem. Ber.* **98**, 1928 (1965).



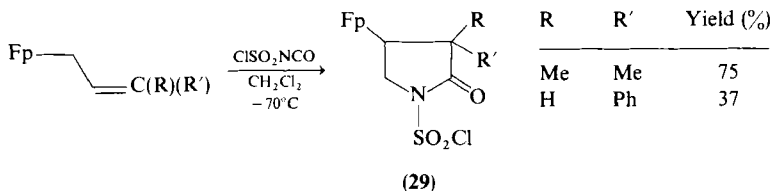
SCHEME 28

cluster compound, $\text{Rh}_6(\text{CO})_{16}$ ⁵⁸ (Scheme 29). The reaction is most selective at low conversions in regard to formation of *N*-cyclopropylpyrrolidone (**25**), but at higher temperatures concomitant reduction by hydrogen (present as an impurity) and cyclopropane ring opening occur. Pyrrolidone (**28**) is the major product when chlorotris(triphenylphosphine)rhodium is used as the catalyst, but it is not clear whether this product is formed by direct carbonylation or by hydrogenolytic cleavage.



SCHEME 29

Pyrrolidones have also been prepared^{59,60} by cycloaddition reactions of monohaptoallyl derivatives of (dicarbonyl)cyclopentadienyliron⁶¹ and related compounds (Scheme 30). Processes of this type provide examples of a



Fp = $\eta^5\text{-C}_5\text{H}_5\text{Fe}(\text{CO})_2$

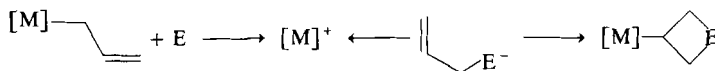
SCHEME 30

⁵⁸ A. F. M. Iqbal, *Tetrahedron Lett.*, 3381 (1971).

⁵⁹ Y. Yamamoto and A. Wojcicki, *Inorg. Nucl. Chem. Lett.* **8**, 833 (1972); *Inorg. Chem.* **12**, 1779 (1973).

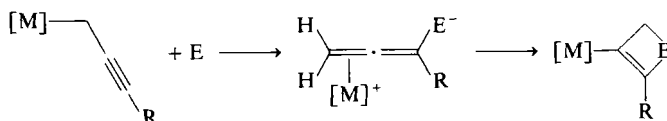
⁶⁰ W. P. Giering, S. Raghu, M. Rosenblum, A. Cutler, D. Ehntholt, and R. W. Fish, *J. Am. Chem. Soc.* **94**, 8251 (1972).

wider class of organometallic reactions in which the monohaptoallyl complex is attacked by an electrophile (E), and the ensuing dipolar intermediate rearranges by displacement of the coordinated alkene.⁶¹ (Scheme 31). Unfortunately from the viewpoint of heterocyclic synthesis, the C—Fe bond in the pyrrolidones **29** is remarkably inert to a variety of reagents (e.g., aq HCl/reflux, KOH/MeOH, HgCl₂, I₂)⁵⁹, although it can be successfully cleaved by thiophenol in the presence of sodium methoxide.⁶⁰

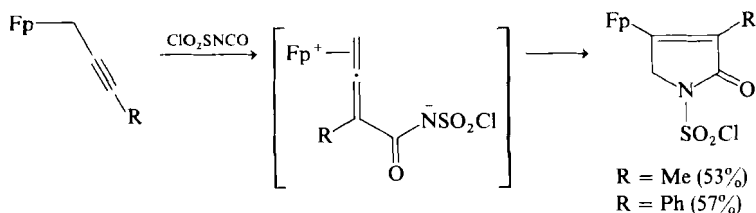


SCHEME 31

The general form of metal-assisted cycloaddition as shown in Scheme 31 can be readily elaborated using monohaptopropargyl complexes (Scheme 32)⁶¹; specific examples illustrating the synthesis of Δ^3 -pyrrolinone derivatives are shown in Scheme 33.⁵⁹



SCHEME 32



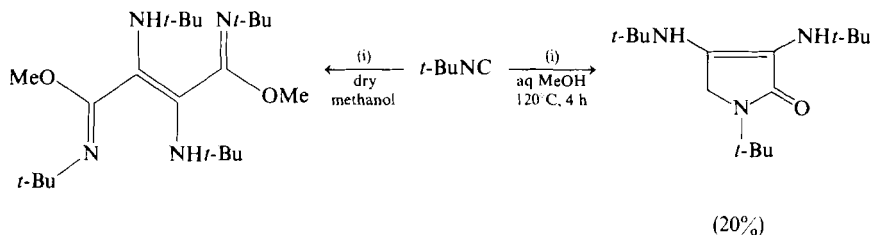
SCHEME 33

Δ^3 -Pyrrolinones have also been obtained from metal-mediated cyclooligomerization processes in which concomitant hydrolytic or carbonyl insertion occurs. For example, *tert*-butyl isocyanide is converted in aqueous methanol by zerovalent nickel compounds e.g., Ni(*t*-BuNC)₄, Ni(CO)₄, into a di(alkylamino)- Δ^3 -pyrrolinone in moderate yield (Scheme 34). The reaction takes a different course in anhydrous methanol in which a di-*tert*-butylaminoethylene derivative is formed, albeit in poor yield (Scheme 34).⁶²

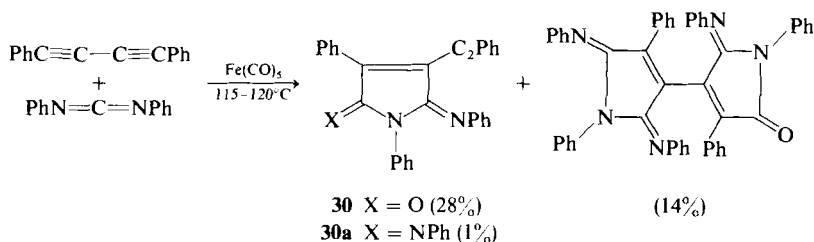
A complex product containing three Δ^3 -pyrrolines is obtained from the cooligomerization of diphenylbutadiyne with diaryl and dicyclohexyl carbo-

⁶¹ M. Rosenblum, *Acc. Chem. Res.* 7, 122 (1974).

⁶² S. Otsuka, A. Nakamura, and K. Ito, *Chem. Lett.*, 943 (1972).

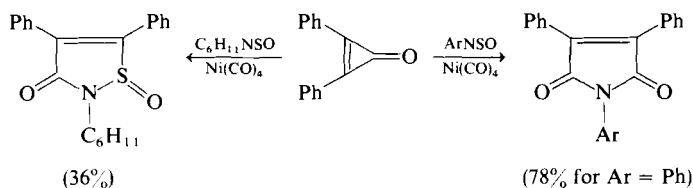
SCHEME 34. (i) $(t\text{-BuNC})_4\text{Ni}$.

diimides in the presence of iron pentacarbonyl⁶³ (Scheme 35). Generally, yields are poor in this type of reaction, but by using iron pentacarbonyl-triphenylphosphine (10:1) as a reactant, the yield of 1,3-diphenyl-4-phenylethynyl-5-phenyliminopyrrolin-2-one (**30a**) is increased to 50%. The Δ^3 -pyrroline products can be quantitatively hydrolyzed in aqueous acid and the procedure offers a useful synthetic route to pyrroline-2,5-diones and bipyrroline-2,2',5,5'-tetraones.



SCHEME 35

Δ^3 -Pyrroline formation with carbonyl insertion also occurs during the reaction of *N*-sulfinylarylamines with diphenylcyclopropenone in the presence of nickel carbonyl (Scheme 36).⁶⁴ Phenyl isocyanate does not give a pyrroline product under these reaction conditions, hence the SO–CO exchange probably occurs within an intermediate metallocycle. The reaction



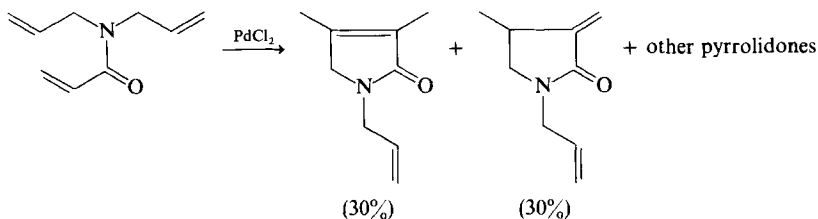
SCHEME 36

⁶³ K. Kinugasa and T. Agawa, *J. Organomet. Chem.* **51**, 329 (1973).

⁶⁴ A. Baba, Y. Oshiro, and T. Agawa, *Chem. Lett.*, 11 (1976).

is sensitive to substituent effects in the sulfinylamine reactant: in contrast to Δ^3 -pyrroline formation from aryl derivatives, the reaction of *N*-sulfinylcyclohexylamine gives rise to an isothiazolone 1-oxide derivative (Scheme 36).

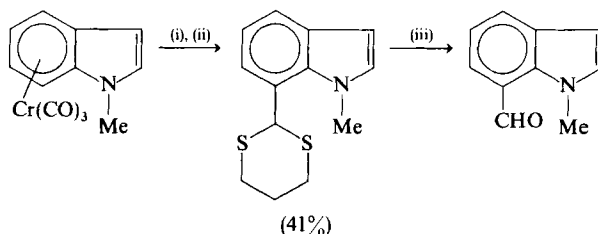
Acrylic acid diallylamide is transformed by palladium chloride into Δ^3 -pyrrolinone derivatives but the synthetic utility of this type of cyclization is limited because of the formation of a complex product mixture containing pyrrolidones (Scheme 37).⁶⁵



SCHEME 37

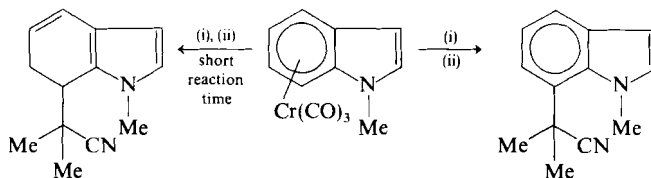
3. Indoles

Two synthetic approaches on intact indoles are notable. In one, the indole substrate is converted into the η^6 -arenetricarbonylchromium complex. The -acetyl and 1-ethoxy-carbonyl derivatives are cleaved to indoles, whereas the 1-methylindole complex undergoes nucleophilic aromatic substitution by 2-lithio-1,3-dithian in a regiospecific manner (Scheme 38).⁶⁶ An analogous reaction occurs with the anion of isobutyronitrile; the latter procedure can be adapted to the synthesis of 6,7-dihydro derivatives (Scheme 39). Restrictions on the method are imposed by the requirement of an *N*-alkyl group, and by the types of anions that can be used for nucleophilic displacement

SCHEME 38. (i) 2-Lithio-1,3-dithian; (ii) aq NH_4Cl ; (iii) Cu^{II} , hydrolysis.

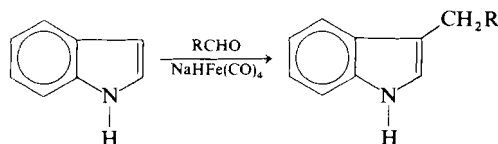
⁶⁵ von E. Schmitz, R. Urban, V. Heuck, G. Zimmerman, and E. Gründemann, *J. Prakt. Chem.* **318**, 185 (1976).

⁶⁶ A. P. Kozikowski and K. Isobe, *J. C. S. Chem. Commun.*, 1076 (1978).

SCHEME 39. (i) $\text{Me}_2\bar{\text{C}}\text{CN}$; (ii) aq NH_4Cl .

(e.g., $\text{Me}\bar{\text{C}}\text{HCO}_2\text{Et}$ and $\text{C}_6\text{H}_{11}\text{N}=\text{CHCH}_2$ do not react). Nevertheless a wider study of this approach for synthesis of benzo- and related heterocycles is warranted.

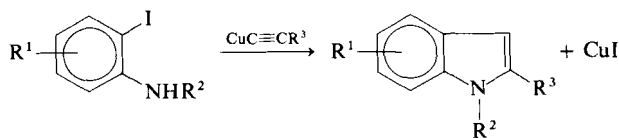
The second method leads to the formation 3-alkyl- and 3-arylindoles from the reaction of indole with aldehydes in the presence of alkali metal tetracarbonylhydridoferrate (Scheme 40).⁶⁷ It is possible that this novel process may occur via reduction of intermediate 3-alkylidene- or 3-arylidene indolenines.



R = e.g., Me, *n*-Pr, Ph
(30–65%)

SCHEME 40

Organometallic complexes of copper, nickel, and palladium have been used in indole syntheses from arenes. Most of the reactions proceed under relatively mild conditions and in some cases give rise to formation of the less common 2-substituted compounds.⁶⁸ Good yields of such 2-substituted derivatives are formed in reactions of *o*-iodoarylamines with cuprous acetylides in dimethylformamide (Scheme 41).⁶⁹ The efficiency of this type of



$\text{R}^1, \text{R}^2 = \text{H, alkyl}; \text{R}^3 = \text{alkyl, aryl}$ (89% for $\text{R}^1 = \text{R}^2 = \text{H}; \text{R}^3 = \text{Ph}$)

SCHEME 41

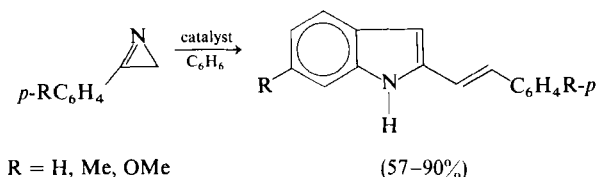
⁶⁷ G. P. Boldrini, M. Panunzio, and A. Umani-Ronchi, *J. C. S. Chem. Commun.*, 359 (1974).

⁶⁸ R. J. Sundberg, "The Chemistry of Indoles." Academic Press, New York, 1970.

⁶⁹ C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.* **31**, 4071 (1966).

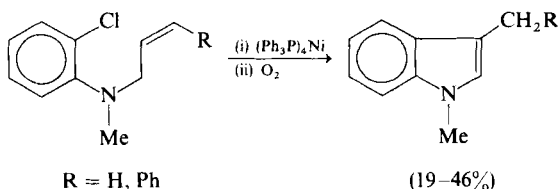
cyclization is solvent-dependent: for example, if pyridine is used, the product can vary from uncyclized *o*-aminoarylacetylide to mixtures containing the desired indole product.

A more complicated type of reaction leading to 2-styrylindoles is observed when 2-arylazirines are treated with the rhodium complexes,⁷⁰ $[(\text{Ph}_3\text{P})_2\text{Rh}(\text{CO})\text{Cl}]$ or $[\text{Rh}(\text{CO})_2\text{Cl}]_2$, or with dicobalt octacarbonyl⁷¹ (Scheme 42). In contrast, 2-arylazirines with molybdenum hexacarbonyl give pyrazines and dihydropyrazines, and with diiron enneacarbonyl give pyrroles (see Sections V,C,2 and IV,A,1, respectively). The use of relatively low molar ratios of 2-arylazirine to rhodium catalyst (2:1) causes the formation of 2,5-diarylpyrroles.



SCHEME 42

1,3-Dialkylindolines and 1,3-dialkylindoles are formed in poor yield (<10%) from the reaction of ethyl- or phenylmagnesium bromide with 2-chloro-*N*-methyl-*N*-allylaniline in the presence of catalytic quantities of (bistriphenylphosphine)nickel dichloride.⁷² In a modification of this procedure, the allyl derivatives can be converted by stoichiometric amounts of tetrakis(triphenylphosphine)nickel into 1,3-dialkylindoles in moderate yield⁷² (Scheme 43); an initial process of oxidative addition and ensuing cyclization of arylnickel intermediates is thought to occur. In contrast to the nickel system,⁷² it has proved possible to achieve the indole synthesis by means of catalytic quantities of palladium acetate.⁷³ It is preferable to use



SCHEME 43

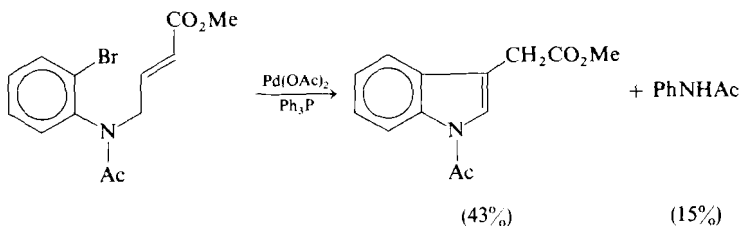
⁷⁰ H. Alper and J. E. Prickett, *J. C. S. Chem. Commun.*, 483 (1976).

⁷¹ H. Alper and J. E. Prickett, *Tetrahedron Lett.*, 2589 (1976).

⁷² M. Mori and Y. Ban, *Tetrahedron Lett.*, 1803 (1976).

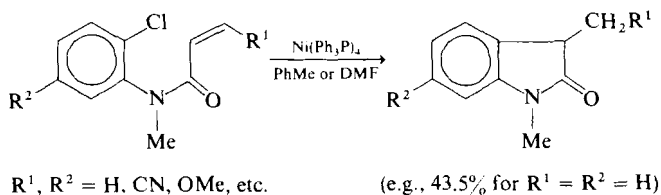
⁷³ M. Mori, K. Chiba, and Y. Ban, *Tetrahedron Lett.*, 1037 (1977).

the aryl bromide, and a base is required to regenerate a palladium(0) species from the presumed palladium hydride product (Scheme 44).⁷³

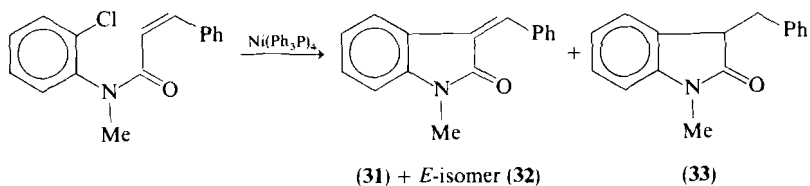


SCHEME 44

This type of indole synthesis can be elaborated to provide a viable route to oxindoles but the type of product is dependent upon the alkene substituent and the reaction solvent ⁷⁴ (Schemes 45 and 46). Assuming that a mechanism



SCHEME 45



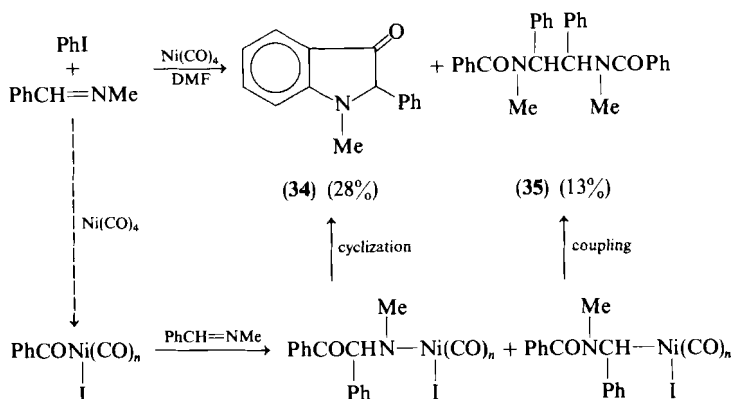
| Yield (%) | | | | |
|-----------|-------|------|------|------|
| Solvent | Total | 31 | 32 | 33 |
| DMF | 86.6 | 55.0 | 10.9 | 20.7 |
| PhMe | 84.0 | 24.3 | 2.3 | 57.4 |

SCHEME 46

⁷⁴ M. Mori and Y. Ban, *Tetrahedron Lett.*, 1807 (1976).

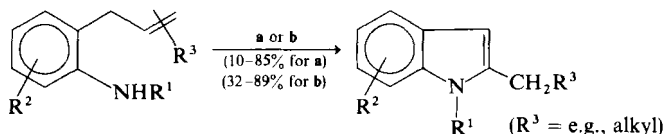
similar to that shown in Scheme 43 applies, it is apparent that elimination of a nickel hydride species competes with an alternative pathway of reductive fission of the Ni(II) intermediate.

A nickel(II) species is also thought to be an intermediate in the carbonylation reaction of iodobenzene with *N*-methylbenzalimine and nickel carbonyl. Two addition modes of an ensuing aroylnickel(II) complex to the C=N double bond can be envisaged as routes to 1-methyl-2-phenylindol-3-one and an ethylenediamine derivative (Scheme 47).⁷⁵ The scope of this simple indole synthesis has not been assessed.



SCHEME 47

A combination of organometallic procedures has been used in the design of a simple, efficient synthesis of 2-alkylindoles from *o*-bromoanilines.⁷⁶ The arylamines are converted in reactions with η^3 -allylnickel dimers⁷⁷ into 2-allylarylamines (36, Scheme 48) which can be cyclized in a separate step



SCHEME 48. Conditions: stoichiometric (a) PdCl₂(MeCN)₂, THF, Et₃N; catalytic (b) PdCl₂(MeCN)₂, benzoquinone, THF, LiCl.

⁷⁵ M. Ryang, Y. Toyoda, S. Murai, N. Sonoda, and S. Tsutsumi, *J. Org. Chem.* **38**, 62 (1973).

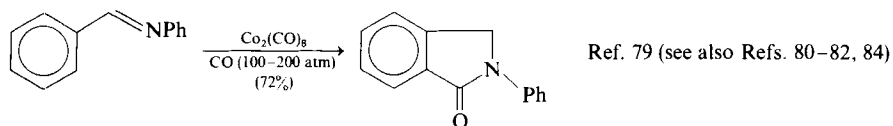
⁷⁶ L. S. Hegedus, G. F. Allen, J. J. Bozell, and E. L. Waterman, *J. Am. Chem. Soc.* **100**, 5800 (1978); L. S. Hegedus, G. F. Allen, and E. L. Waterman, *ibid.* **98**, 2674 (1976).

⁷⁷ Cf. L. S. Hegedus, in "New Applications of Organometallic Reagents in Organic Synthesis" (D. Seyferth, ed.), p. 329. Elsevier, Amsterdam, 1976.

using palladium(II) salts in either stoichiometric or catalytic quantities. Useful features of this type of process are the tolerance of functional groups to the catalyst (e.g., CO_2R , $\text{N}-\text{Ac}$) and its elaboration to the preparation of related condensed pyrroles.⁷⁶

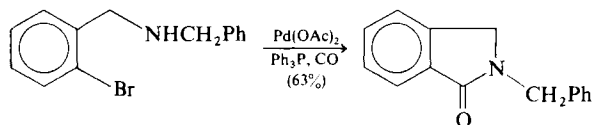
4. Isoindoles

The synthesis of phthalimidines by dicobalt octacarbonyl-catalyzed carbonylation of Schiff bases was first described by Pritchard⁷⁸ and the scope of the reaction was evaluated by Murahashi *et al.*⁷⁹ Later Rosenthal *et al.*⁸⁰⁻⁸³ subjected a variety of related compounds to carbonylation, and also achieved a phthalimidine synthesis directly from benzonitrile under the conditions of the oxo process.⁸⁴ An example illustrating the formation of a phthalimidine is shown in Scheme 49; a comprehensive review of the scope and mechanism of reactions of this type is available.⁸⁵



SCHEME 49

Isoindolin-1-ones can also be prepared by the palladium-mediated carbonylation of *o*-bromo(aminoalkyl)benzenes (Scheme 50).⁸⁶ This amidation



SCHEME 50

⁷⁸ W. W. Pritchard, U.S. Patent 2,841,591 (1958) [*CA* **52**, 20197 (1958)].

⁷⁹ S. Murahashi and S. Horiie, *J. Am. Chem. Soc.* **77**, 6403 (1955); S. Murahashi, S. Horiie, and T. Joh, *Bull. Chem. Soc. Jpn.* **33**, 81 (1960).

⁸⁰ A. Rosenthal, R. F. Astbury, and A. Hibscher, *J. Org. Chem.* **23**, 1037 (1958).

⁸¹ A. Rosenthal and M. R. S. Weir, *Can. J. Chem.* **40**, 610 (1962).

⁸² A. Rosenthal and S. Millward, *Can. J. Chem.* **41**, 2504 (1963).

⁸³ A. Rosenthal and M. R. S. Weir, *J. Org. Chem.* **28**, 3025 (1963).

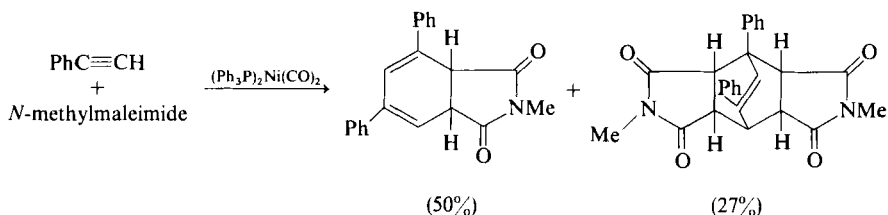
⁸⁴ A. Rosenthal and J. Gervay, *Chem. Ind. (London)*, 1623 (1963).

⁸⁵ A. Rosenthal and I. Wender, in "Organic Synthesis Via Metal Carbonyls" Vol. 1 (I. Wender and P. Pino, eds.), p. 405. Wiley (Interscience), New York, 1968.

⁸⁶ M. Mori, K. Chiba, and Y. Ban, *J. Org. Chem.* **43**, 1684 (1968).

procedure is attractive because high pressures of carbon monoxide are not required and catalytic quantities of palladium acetate are used; the method can be employed to provide a facile synthesis of six and seven-membered ring benzolactams.⁸⁶

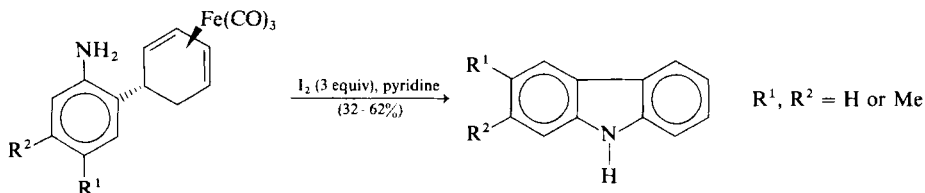
Reduced isoindoles are formed when acetylenes are cooligomerized with *N*-phenyl- or *N*-methylmaleimide but the synthetic value of these processes is limited by competing secondary reactions of product cycloaddition (Scheme 51) and oxidation.⁸⁷



SCHEME 51

5. Carbazoles

Tricarbonyl(cyclohexadienyl)iron cations react with a variety of nucleophiles to give substituted tricarbonyl(cyclohexadienyl)iron complexes⁸⁸; with arylamines, *N*- or *C*-alkylation can occur depending on the nature of aryl ring substituents. Deligation of *C*-alkylated arylamines can be achieved by either ferric chloride, which gives the free arylamine, or by iodine; in the latter case, cyclization with concomitant oxidation occurs, and carbazoles are produced in moderate yield (Scheme 52).⁸⁹



SCHEME 52

⁸⁷ A. J. Chalk, *J. Am. Chem. Soc.* **94**, 5928 (1972).

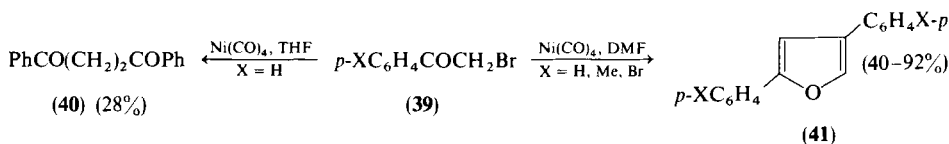
⁸⁸ A. J. Birch and I. D. Jenkins, *Org. Chem. (N.Y.)* **33**, pt. *Synth.* 1, 41 (1976).

⁸⁹ A. J. Birch, A. J. Liepa, and G. R. Stephenson, *Tetrahedron Lett.*, 3565 (1979).

B. WITH OXYGEN AS HETEROATOM

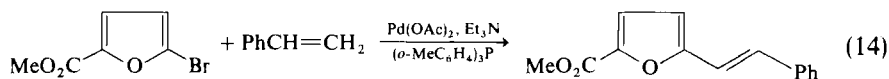
1. *Furans*

The course of the reaction of phenacyl bromides (**39**) with nickel carbonyl is markedly dependent on the solvent employed: in tetrahydrofuran the products are 1,2-dibenzoyl ethanes (cf. **40**) but in dimethylformamide, 2,5-diarylfurans (**41**) are obtained in moderate to excellent yield (Scheme 53).⁹⁰ It is possible that the furan derivatives (**41**) arise via intermediate β,γ -epoxyketones which can be isolated as products from a number of α -bromo-ketone substrates [cf. **39** and Section II].²⁸



SCHEME 53

Alkenylfurans can be prepared by coupling of bromofurans with styrene (Eq. 14).⁹¹ This type of process (Eq. 14) is a logical extension of analogous reactions of aryl,⁹² vinyl^{92,93} and benzylic halides,⁹² and has been successfully applied to a variety of heterocyclic halides.⁹¹

2. *Reduced Furans*

The synthesis of tetrahydrofuran derivatives from unsaturated alcohols via hydroformylation intermediates was developed many years ago. Moderate yields are obtained from but-2-en-1,4-diol (Scheme 54)⁹⁴ but hydroformylation is not the major pathway when coniferyl alcohol is subjected to the oxo process (Scheme 55).⁹⁵ A more complicated reaction is involved

⁹⁰ E. Yoshisato and S. Tsutsumi, *Chem. Commun.*, 33 (1968).

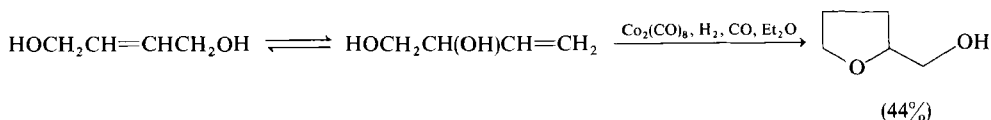
⁹¹ W. C. Frank, Y. C. Kim, and R. F. Heck, *J. Org. Chem.* **43**, 2947 (1978).

⁹² H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.* **96**, 1133 (1974).

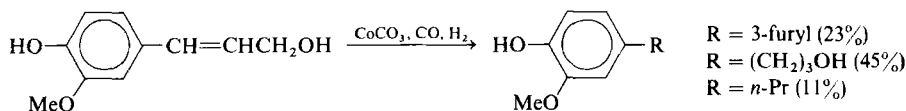
⁹³ H. A. Dieck and R. F. Heck, *J. Org. Chem.* **40**, 1083 (1975).

⁹⁴ L. E. Craig, R. M. Elofson, and I. J. Ressa, *J. Am. Chem. Soc.* **72**, 3277 (1950).

⁹⁵ L. S. Nahum, *J. Org. Chem.* **33**, 3601 (1978).

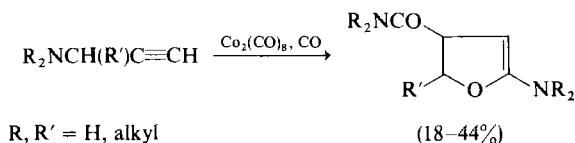


SCHEME 54



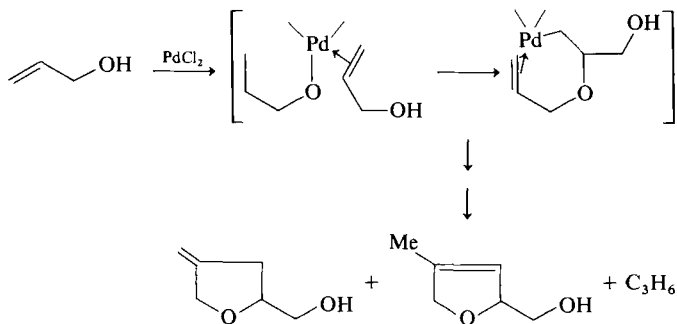
SCHEME 55

in the cobalt carbonyl-catalyzed carbonylation of aminopropyne derivatives in which dihydrofurans are formed (Scheme 56).⁹⁶ This type of process is unusual since acetylenes are normally converted into dimeric lactones (bifurandiones) under these reaction conditions (see Section IV,B,3).



SCHEME 56

Reduced furans are formed in two types of oxypalladation processes on substrate α,β - and γ,δ -unsaturated alcohols. In an unusual reaction, allyl alcohol is converted into 4-methylenetetrahydrofurfuryl alcohol, among other products (Scheme 57)⁹⁷; the formation of propene is thought to arise by reductive hydrogenolysis of allyl alcohol.

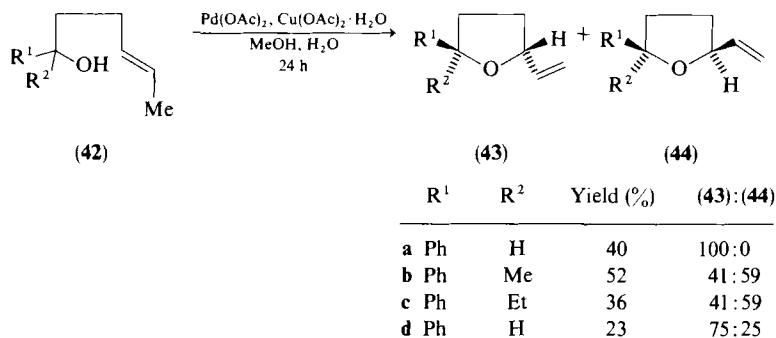


SCHEME 57

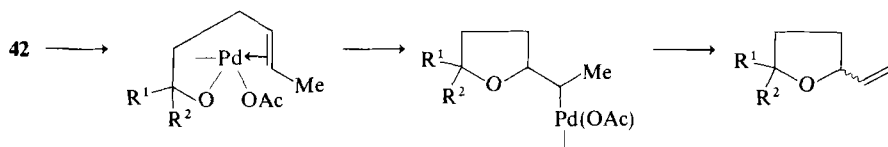
⁹⁶ J. C. Sauer, *J. Am. Chem. Soc.* **81**, 693 (1959).

⁹⁷ W. Hafner, H. Prigge, and J. Smidt, *Justus Liebigs Ann. Chem.* **693**, 109 (1966).

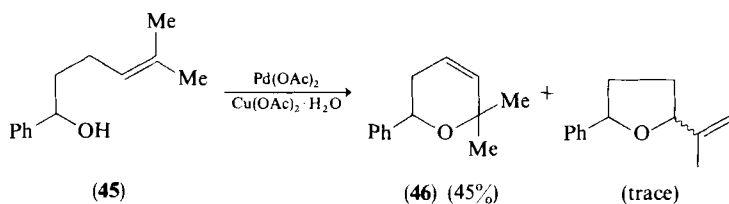
An interesting feature of the cyclization of γ,δ -unsaturated alcohols is the marked effect on product isomer distribution by the nature of substituents remote from the double bond (cf. **42** and Scheme 59).⁹⁸ Complete stereospecificity is observed for the phenyl derivative **42a** in contrast to **42b** and **c**, and the isomer ratio is reversed for **42d**. The suggested mechanism⁹⁸ is shown in Scheme 60: the trisubstituted alkene (**45**) is mainly converted into a pyran (**46**) rather than a tetrahydrofuran derivative (Scheme 61).



SCHEME 59



SCHEME 60



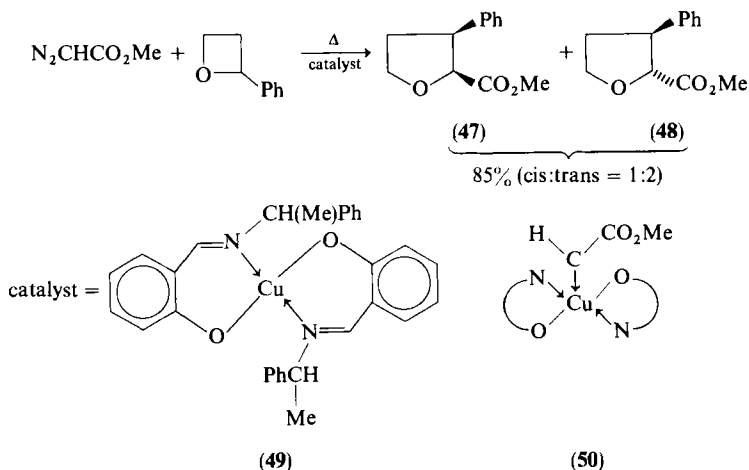
SCHEME 61

Isomeric tetrahydrofuran derivatives (**47** and **48**) are formed by copper(II)-catalyzed decomposition of methyl diazoacetate in 2-phenyloxetan (Scheme 62).⁹⁹ Use of the chiral homogeneous catalyst, bis[*N*-(*R*)- α -phenylethylsalicylaldiminato]copper(II) (**49**),¹⁰⁰ causes asymmetric induction albeit with

⁹⁸ T. Hosokawa, M. Hirata, S. Murahashi, and A. Sonada, *Tetrahedron Lett.*, 1821 (1976); see also T. Hosokawa, H. Ohkita, and I. Moritani, *Bull. Chem. Soc. Jpn.*, 48, 1533 (1975).

⁹⁹ H. Nozaki, S. Moriuti, H. Takaya, and R. Noyori, *Tetrahedron Lett.*, 5239 (1966).

¹⁰⁰ L. Sacconi and M. Ciampolini, *J. Chem. Soc.*, 276 (1964).



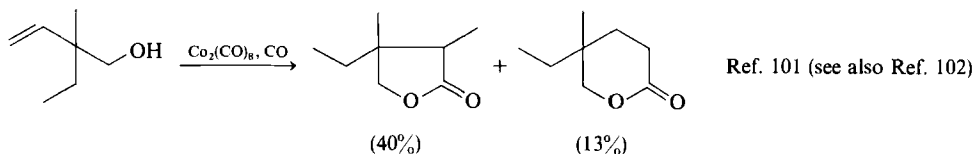
SCHEME 62

relatively low enantiomeric excess values; the intermediacy of a chiral copper-carbene complex (**50**) is tentatively proposed.⁹⁹

3. Furan-2-ones (*Butenolides and Butyrolactones*)

The hydrocarboxylation of suitably substituted hydroxyalkylacetylenes and alkenes has been widely used to prepare a variety of butenolides and butyrolactones (see Scheme 63^{101,102} and Refs. 8 and 10a for reviews of earlier literature); a closely related reaction is shown in Scheme 64.^{103,104}

In a more complex type of reaction, propene reacts with methyl trichloroacetate under the catalytic influence of cyclopentadienylmolybdenum tricarbonyl or cyclopentadienyliron dicarbonyl dimers to give 4-methyl-2,2'-



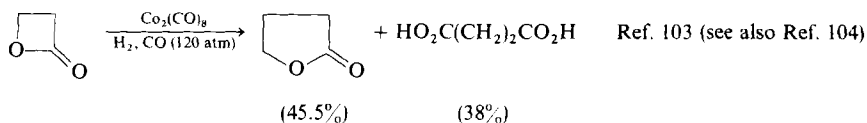
SCHEME 63

¹⁰¹ J. Falbe, H. J. Schulze-Steinen, and F. Korte, *Chem. Ber.* **98**, 886 (1965).

¹⁰² J. R. Norton, K. E. Shenton, and J. Schwartz, *Tetrahedron Lett.*, 51 (1975).

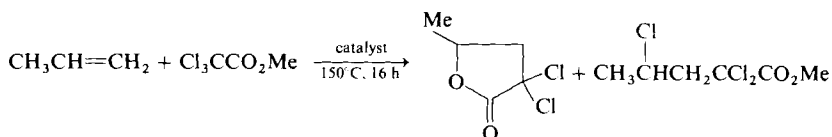
¹⁰³ Y. Mori and J. Tsuji, *Bull. Chem. Soc. Jpn.* **42**, 777 (1969).

¹⁰⁴ T. A. Pudova, F. K. Velichko, L. V. Vinogradova, and R. Kh. Friedlina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 116 (1975) [*Engl. Transl.*, 104 (1975)].



SCHEME 64

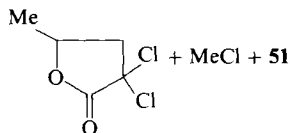
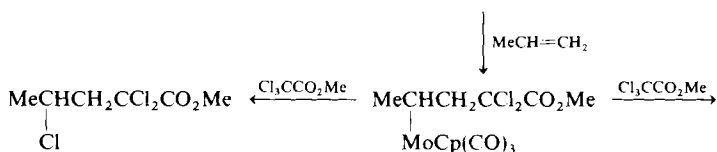
dichloro- γ -butyrolactone (Scheme 65)¹⁰⁵; this type of process can be extended to the preparation of a variety of 4-alkyl and 4,4'-dialkyl analogs in reasonable yield (42–74%).¹⁰⁵ The efficiency of cyclization to the lactone product (Mo versus Fe) is thought to reflect the different degree of coordinative interaction within intermediate (cyclopentadienyl)alkylmetal complexes (cf. **52** in Scheme 66).¹⁰⁵ Transformations of the type **51** \rightarrow **52** are unprecedented in the chemistry of organometallic insertion reactions.¹⁰⁶



SCHEME 65



(51)



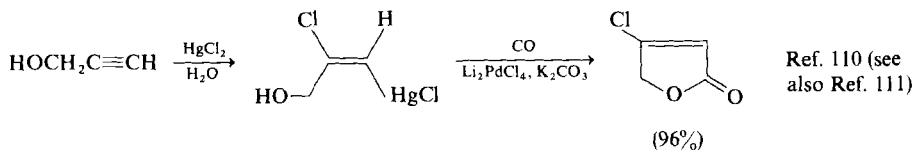
SCHEME 66

Synthetic methods leading to $\Delta^{\alpha,\beta}$ -butenolides are of particular interest because of the wide range of biological activities exhibited by naturally

¹⁰⁵ Y. Mori and J. Tsuji, *Tetrahedron* **28**, 29 (1972).

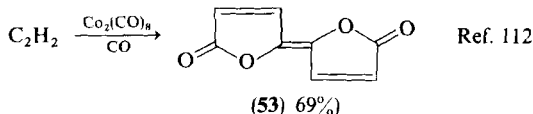
¹⁰⁶ Cf. K. J. Ivin, J. J. Rooney, C. D. Stewart, M. L. H. Green, and R. Mahtab, *J. C. S. Chem. Commun.*, 604 (1978).

occurring compounds in this category.¹⁰⁷⁻¹⁰⁹ A procedure involving the carbonylation of an organopalladium intermediate is shown in Scheme 67¹¹⁰; high yields are obtained and the starting acetylenic alcohols are readily available.

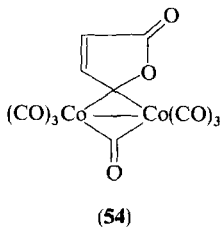


SCHEME 67

A more complex carbonylation process is involved in the formation of bisbutenolides (bifurandiones) from cobalt carbonyl-catalyzed carbonylation of alkynes¹¹²⁻¹¹⁷ (Scheme 68). The trans derivative (**53**) is formed in good yield from acetylene,¹¹² but yields from substituted acetylenes (e.g., propyne)



SCHEME 68



¹⁰⁷ L. J. Haynes, *Q. Rev., Chem. Soc.* **2**, 46 (1948).

¹⁰⁸ B. L. Van Duuren, *Ann. N.Y. Acad. Sci.* **163**, 633 (1969).

¹⁰⁹ A. Dal Pozzo, A. Dansi, and E. Meneghini, *Boll. Chim. Farm.* **113**, 280 (1974).

¹¹⁰ R. C. Larock and B. Riefling, *Tetrahedron Lett.*, 4661 (1976).

¹¹¹ A. Cowell and J. K. Stille, *Tetrahedron Lett.*, 133 (1979).

¹¹² J. C. Sauer, R. D. Cramer, V. A. Engelhardt, T. A. Ford, H. E. Holmquist, and B. W. Howk, *J. Am. Chem. Soc.* **81**, 3677 (1959).

¹¹³ J. C. Sauer, U. S. Patent 2,840,570 (1958).

¹¹⁴ G. Albanesi and M. Tovaglieri, *Chim. Ind. (Milan)* **41**, 189 (1959).

¹¹⁵ G. Albanesi, *Chim. Ind. (Milan)* **46**, 1169 (1964).

¹¹⁶ G. Albanesi, R. Farina, and A. Taccioli, *Chim. Ind. (Milan)* **48**, 1151 (1966).

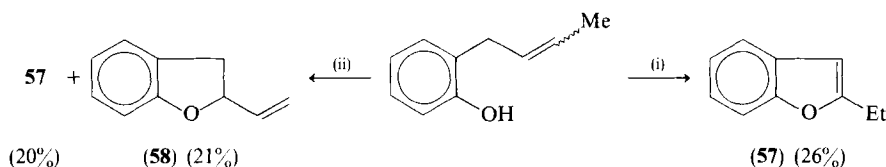
¹¹⁷ D. J. S. Guthrie, I. U. Khand, G. R. Knox, J. Kollmeier, P. L. Pauson, and W. E. Watts, *J. Organomet. Chem.* **90**, 93 (1975).

are very low and three regioisomers are produced.¹¹⁷ It is probable that the bifurandione derivatives are formed via cobalt complexes in which butenolactone groups act as bridging carbene ligands (cf. **54** and Refs. 117 and 118).

4. Benzofurans

2-Allylphenol can be converted into 2-methylbenzofuran only under forcing conditions (Pd/C, 500–800°C)¹¹⁹ hence the more recent method of intramolecular oxypalladation provides a valuable general synthesis of 2-substituted derivatives in this category. In early studies it was shown that sodium salts of allylphenols will react in a stoichiometric manner with dichlorobis(benzonitrile)palladium(II) to give the 2-substituted compounds in moderate yield.^{120,121} Palladium acetate is a more useful reagent since the free phenol can be used, but the method suffers from the disadvantage that two benzofuran isomers are formed (Scheme 70).¹²¹ The product isomer ratio (**57**:**58**) is affected by the molar ratio of allylphenol derivative to palladium acetate but the reason for this is unclear. The reaction mode can also be influenced by adding sodium salts of carboxylic acids where cyclization to six-membered ring compounds can be induced in preference to five- (see Section V,B,2).¹²²

It is of particular value from a synthetic viewpoint that, under Wacker-type conditions the cyclization is catalytic [$\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2/\text{MeOH}, \text{H}_2\text{O}/\text{air}/55^\circ\text{C}$]¹²¹ albeit not by a Wacker-type mechanism.¹²³ Addition of the chiral alkene, (–)- β -pinene, to the catalyzed cyclization of 2-(but-2-enyl)phenol causes asymmetric induction with an optical yield of 12%



SCHEME 70 (i) $(\text{PhCN})_2\text{PdCl}_2$, NaOMe; (ii) $\text{Pd}(\text{OAc})_2$.

¹¹⁸ P. A. Elder, D. J. S. Guthrie, J. A. D. Jeffreys, G. R. Knox, J. Kollmeier, P. L. Pauson, D. A. Symon, and W. E. Watts, *J. Organomet. Chem.* **120**, C13 (1976).

¹¹⁹ C. Hansch, W. Saltonstall, and J. Settle, *J. Am. Chem. Soc.* **71**, 943 (1949).

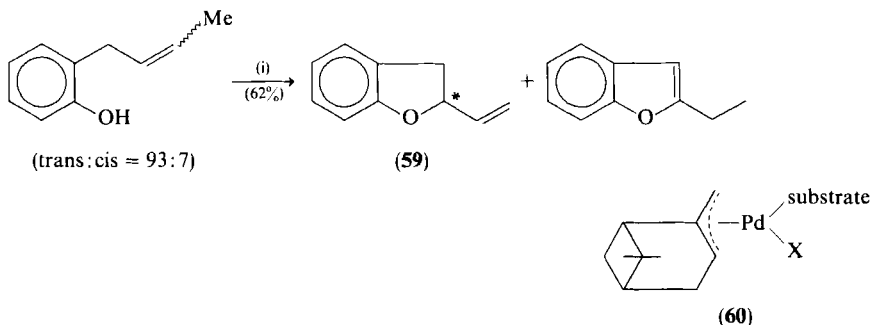
¹²⁰ T. Hosokawa, K. Maeda, K. Koga, and I. Moritani, *Tetrahedron Lett.*, 739 (1973).

¹²¹ T. Hosokawa, H. Ohkata, and I. Moritani, *Bull. Chem. Soc. Jpn.* **48**, 1533 (1975).

¹²² T. Hosokawa, S. Yamashata, S. Murahashi, and A. Sonoda, *Bull. Chem. Soc. Jpn.* **49**, 3662 (1976).

¹²³ T. Hosokawa, T. Uno, and S. Murahashi, *J. C. S. Chem. Commun.*, 475 (1979).

(Scheme 71).¹²⁴ An intermediate π -allylpalladium species (**60**) is thought to effect this transformation and in this context it is significant that presynthesized bis[acetoxyl(7,1,2)- η -pinene]palladium(II)]¹²⁵ reacts in a similar fashion, affording optically active **59** in comparable optical yield.¹²⁴



SCHEME 71. (i) Pd(OAc)₂, Cu(OAc)₂ · H₂O, (-)-β-pinene, O₂.

Selective transfer hydrogenation of one carbonyl group of cyclohexane-1,3-diones can be achieved using ethylene glycol as a hydrogen donor and RuCl₂(PPh₃)₂ as a catalyst.¹²⁶ If the hydroxyacetaldehyde produced accumulates it reacts with more 1,3-dione to give the 3,5,6,7-tetrahydro-4(2H)-benzofuranone (cf. **62**) in moderate yield¹²⁷ (Scheme 73); the ruthenium catalyst may operate in more than one step. With the exception of the Claisen rearrangement of 3-allyloxy-2-cyclohexen-1-ones,¹²⁸ the known syntheses of benzofuranones of type **62** (R = H) and simple alkyl derivatives are inefficient and generally give impure products.¹²⁹⁻¹³³

Benzofurans have also been prepared by the coupling of *o*-halogenophenols with cuprous aryl acetylides and ensuing cyclization of intermediate diarylacetylides¹³⁴⁻¹³⁶ (Scheme 74).

¹²⁴ T. Hosokawa, S. Miyagi, S. Murahashi, and A. Sonoda, *J. C. S. Chem. Commun.*, 687 (1978).

¹²⁵ Cf. B. M. Trost and P. E. Strege, *Tetrahedron Lett.*, 2603 (1974).

¹²⁶ Y. Sasson, J. Blum, and E. Dunkelblum, *Tetrahedron Lett.*, 3199 (1973).

¹²⁷ P. Albin, J. Blum, E. Dunkelblum, and Y. Sasson, *J. Org. Chem.*, **40**, 2402 (1975).

¹²⁸ Y. Tamura, Y. Kita, M. Shimagaki, and M. Terashima, *Chem. Pharm. Bull.*, **19**, 571 (1971).

¹²⁹ N. Nicki, *Chem. Ber.*, **91**, 553 (1958).

¹³⁰ F. Korte, D. Scharf, and K. H. Büchel, *Justus Liebigs Ann. Chem.*, **664**, 97 (1963).

¹³¹ S. Vemura, T. Nakano, and K. Ichikawa, *Nippon Kagaku Zasshi*, **89**, 203 (1968).

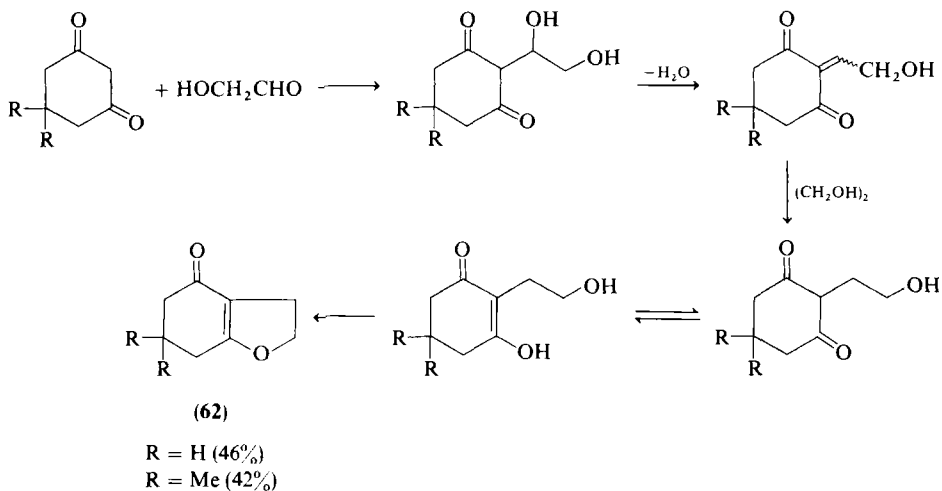
¹³² K. Ichikawa, O. Itoh, and T. Kawamura, *Bull. Chem. Soc. Jpn.*, **41**, 1240 (1960).

¹³³ J. M. McIntosh and P. M. Beaumier, *Can. J. Chem.*, **51**, 843 (1973).

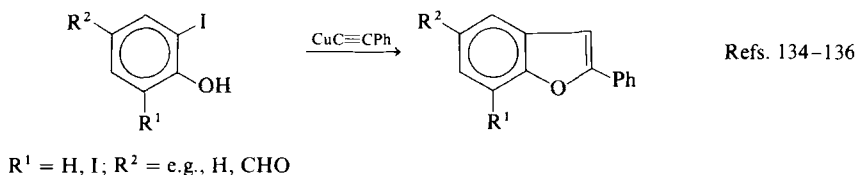
¹³⁴ R. D. Stephens and C. E. Castro, *J. Org. Chem.*, **28**, 3313 (1963).

¹³⁵ C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **31**, 4071 (1966).

¹³⁶ M. T. Cox and J. J. Holohan, *Tetrahedron*, **31**, 633 (1975).

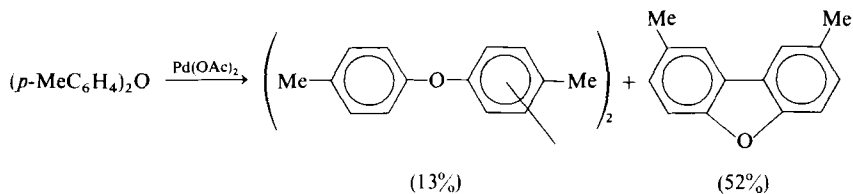


SCHEME 73



SCHEME 74

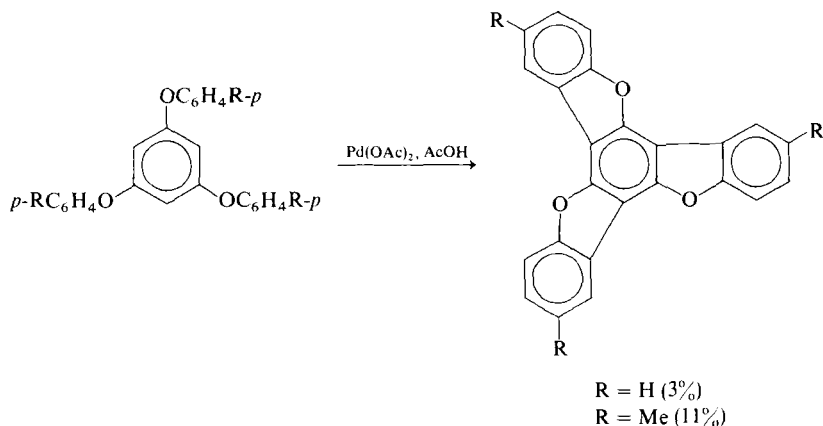
Dibenzofurans can be synthesized by the intramolecular dehydrogenative coupling of diaryl ethers in the presence of catalytic amounts of palladium acetate under a pressure of oxygen; the formation of dimeric ethers as intermolecular condensation products is a competing process¹³⁷ (Scheme 75). From an investigation of product ratios and from competitive coupling experiments, it appears likely that the mechanism leading to dibenzofuran



SCHEME 75

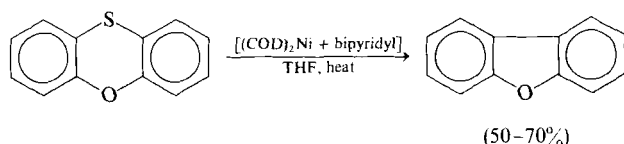
¹³⁷ A. Shiotani and H. Itatani, *J. C. S. Perkin I*, 1236 (1976).

formation is akin to the intermolecular coupling of aryl compounds.¹³⁸ A related reaction leading to a condensed dibenzofuran derivative is illustrated in Scheme 76.¹³⁹



SCHEME 76

Dibenzofuran is also formed when phenoxathiin is desulfurized by bis(1,5-cyclooctadiene)nickel(0) and 2,2'-bipyridyl, but limited synthetic application can be envisaged for this type of reaction despite the high yield obtained (see Scheme 77).¹⁴⁰



SCHEME 77

5. Isobenzofurans

Diarylthioketones are converted in good yields into orthometallated complexes by diiron enneacarbonyl.¹⁴¹ These in turn can be transformed oxidatively (Ce^{4+}) or photochemically into isobenzothiophenes (see Section IV.C.2), or by reaction with mercuric trifluoroacetate into isobenzofurans (Scheme 78)¹⁴²; the formation of methoxy esters is a competing process in

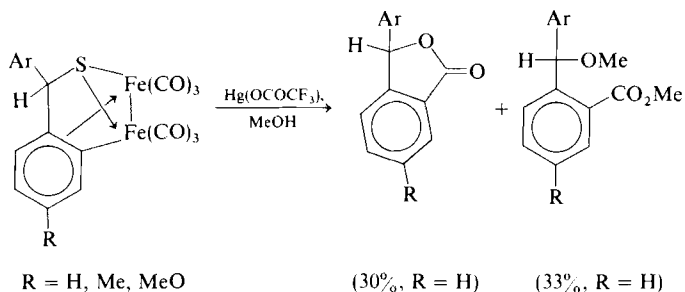
¹³⁸ R. van Helden and G. Verberg, *Recl. Trav. Chim. Pays-Bas* **84**, 1263 (1965).

¹³⁹ J. Bergman and B. Egestad, *Tetrahedron Lett.*, 3143 (1978).

¹⁴⁰ J. J. Eisch and R. I. Kyoung, *J. Organomet. Chem.* **139**, C51 (1977).

¹⁴¹ H. Alper and A. S. K. Chan, *Chem. Commun.*, 1203 (1971).

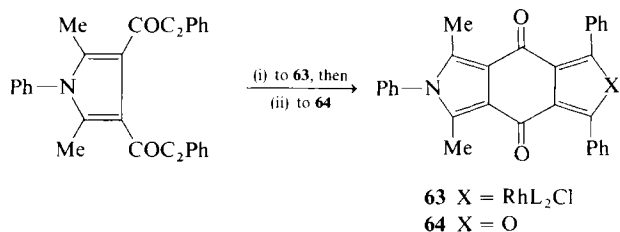
¹⁴² H. Alper and W. G. Root, *J. Am. Chem. Soc.* **97**, 4251 (1975).



SCHEME 78

reactions of the latter type. It would be of interest to evaluate the behavior of nitrogen-centered nucleophilicities in this unusual type of synthesis.

The condensed isobenzofuran derivative 1,3-dimethyl-2,5,7-triphenyl-2H-furo[3,4-*f*]isoidoloquinone (**64**), has been prepared in four steps from a pyrrole derivative¹⁴³ (Scheme 79); a thiophene analog of **64** has been obtained in a similar manner.¹⁴⁴ Key intermediates in both types of reactions are condensed rhodacyclopentadienes (cf. **63**) which are obtained from appropriate diynes.

SCHEME 79 (i) L_3RhCl ; (ii) 30% H_2O_2 .

C. WITH SULFUR AS HETEROATOM

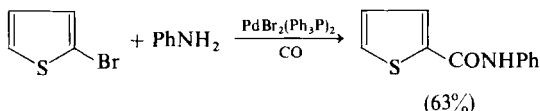
1. Thiophenes

Dibromobistriphenylphosphinepalladium(II) is an effective carbonylation catalyst in the reaction of 2-bromothiophene with aniline¹⁴⁵ (Scheme 80); acylpalladium species are presumably intermediates in this type of reaction, which can also be used to prepare pyridine derivatives. 2-Bromothiophene

¹⁴³ E. Müller and W. Winter, *Chem. Ber.* **105**, 2523 (1972).

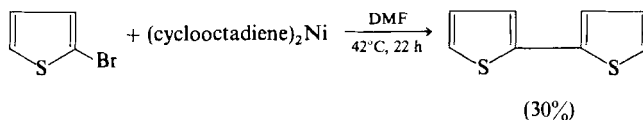
¹⁴⁴ E. Müller and W. Winter, *Justus Liebigs Ann. Chem.*, 605 (1975).

¹⁴⁵ A. Schoenberg and R. F. Heck, *J. Org. Chem.* **39**, 3327 (1974).



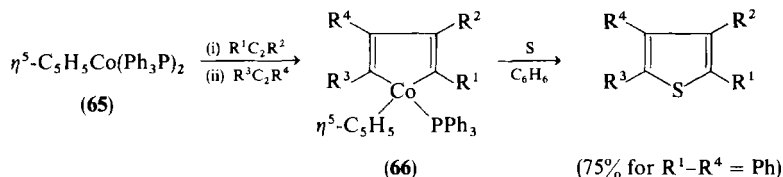
SCHEME 80

can also be caused to couple by bis(cyclooctadiene)nickel(0) under relatively mild conditions (Scheme 81),¹⁴⁶ presumably via a dihetarylnickel dibromide intermediate. This type of transformation can be applied to substrates containing a variety of functional groups (ketone, aldehyde, ester, nitrile) and is thus preferred to the two-step coupling method involving reactions of aryl Grignard or lithium reagents with metal salts; the alternative Ullmann procedure requires relatively high temperatures.



SCHEME 81

A direct synthesis of the thiophene nucleus has been achieved by allowing air-stable cobaltacyclopentadiene complexes (**66**) to react with sulfur; the organometallic complexes are prepared in variable yields in a stepwise fashion from η^5 -cyclopentadienylbis(triphenylphosphine)cobalt (**65**) (Scheme 82).^{147,148} Reactions of the complexes **66** with selenium and nitrosobenzene give rise to selenophenes and pyrroles, respectively.



SCHEME 82

An alternative, rather esoteric direct thiophene synthesis is illustrated in Scheme 83, in which a structurally novel¹⁴⁹ thiaphosphanorbornadiene complex (**67**) is pyrolyzed under a pressure of carbon monoxide.¹⁵⁰

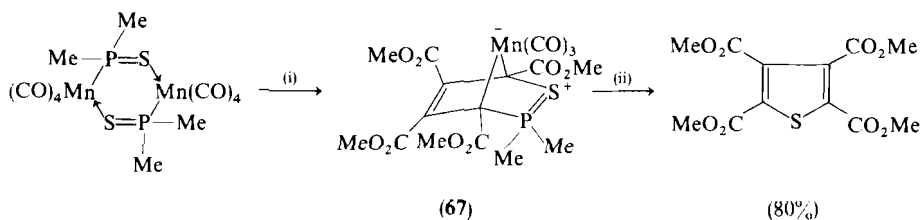
¹⁴⁶ M. F. Semmelhack, P. M. Helquist, and L. D. Jones, *J. Am. Chem. Soc.* **93**, 5908 (1971).

¹⁴⁷ Y. Wakatsuki, T. Kuramitsu, and H. Yamazaki, *Tetrahedron Lett.*, 4549 (1974).

¹⁴⁸ For analogous transformations on dinuclear iron complexes, see E. H. Braye and W. Hübel, *Chem. Ind. (London)*, 1250 (1959).

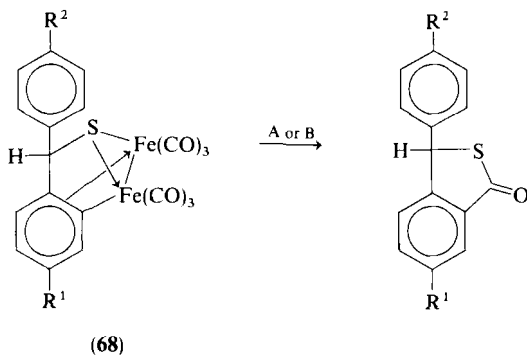
¹⁴⁹ E. Linder and B. Schilling, *Chem. Ber.* **110**, 3889 (1977).

¹⁵⁰ E. Linder, A. Ran, and S. Hoehne, *Angew. Chem., Int. Ed. Engl.* **18**, 534 (1979).

SCHEME 83. (i) $\text{MeO}_2\text{CC}\equiv\text{CCO}_2\text{Me}$; (ii) CO, THF.

2. Isobenzothiophenes

Diaryl thioketones are converted by diiron enneacarbonyl into products of orthometallation.¹⁴¹ Oxidative or photochemically induced deligation of these complexes provides an unusual and valuable synthetic entry into compounds in the uncommon isobenzothiophene category^{142,151} (Scheme 84). Moreover, the photochemical procedure provides the novel complex, (tetracyanoethylene)tetracarbonyl iron. The orthometallated complexes (68) can also be used to prepare isobenzofurans (see Section IV,B,5).



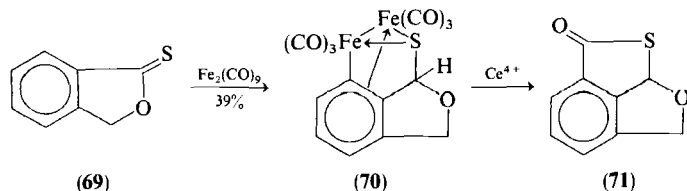
$\text{R}^1, \text{R}^2 = \text{e.g., H, OMe, CF}_3$ (66% for $\text{R}^1 = \text{R}^2 = \text{OMe}$)

SCHEME 84. (A) Ce^{IV} , Me_2CO ; (B) hv, TCNE.

It is interesting to note that orthometallation occurs preferentially at the aryl ring in the thiolactone **69** despite the availability of oxygen as a potential donor ligand; oxidation of the dinuclear complex **70** by ceric ion gives the condensed isobenzothiophene derivative **71** in unspecified yield¹⁵² (Scheme 85).

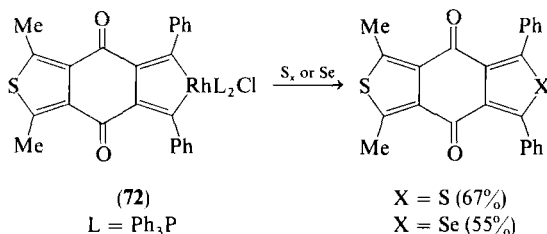
¹⁵¹ H. Alper and A. S. K. Chan, *J. Am. Chem. Soc.* **95**, 4905 (1973).

¹⁵² H. Alper and C. F. Foo, *Inorg. Chem.* **14**, 2928 (1975).



SCHEME 85

A series of condensed isobenzothiophene derivatives has been synthesized^{144,153,154} from the rhodacyclopentadieno[3'.4':4.5]benzo[1,2-c]thiophen-4,8-quinone (72) (see Scheme 86 and Section IV,B,5 for details of the preparation of rhodium complexes analogous to 72).



SCHEME 86

D. WITH TWO HETEROATOMS (N,N)

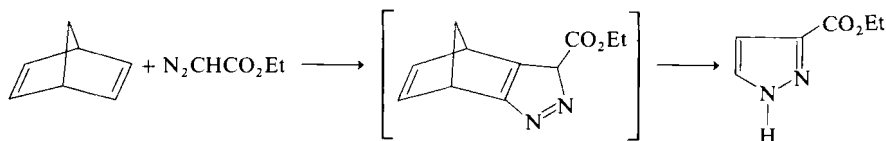
1. Pyrazoles

Pyrazoles can be synthesized by thermal cycloreversion of adducts formed in the 1,3-dipolar cycloaddition of alkyl diazoacetates with norbornadiene. The rate of the primary process of cycloaddition is accelerated by iron pentacarbonyl (Scheme 88)¹⁵⁵; a similar catalytic effect has been observed during the formation of ethyl 5-phenyl- Δ^2 -pyrazoline-3-carboxylate from cycloaddition of ethyl diazoacetate and styrene.¹⁵⁵ Reactions of this type are catalyzed presumably because of coordination of one or both reactants to the transition metal, and a wider study of the effect of a variety of complexes on 1,3-dipolar cycloaddition processes would be valuable.

¹⁵³ E. Müller, E. Luppold, and W. Winter, *Chem. Ber.* **108**, 237 (1975).

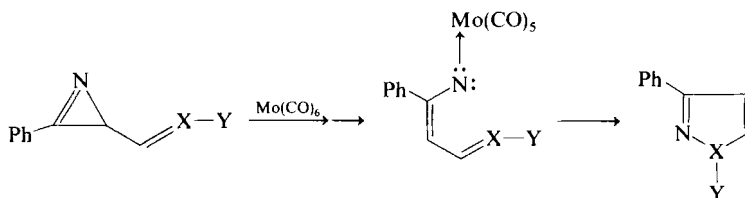
¹⁵⁴ For a review describing the scope of the diyne synthesis, see E. Müller, *Synthesis*, **11**, 761 (1974).

¹⁵⁵ R. Paulissen, *J. C. S. Chem. Commun.*, 219 (1976).

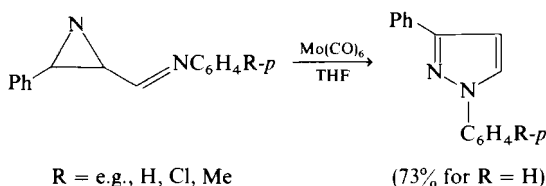


SCHEME 88. Conditions: (i) 25°C , 4 weeks; (ii) 25°C , 3 days, $\text{Fe}(\text{CO})_5$ or $\text{Co}_2(\text{CO})_8$.

A variety of heterocyclic compounds including pyrroles and pyrazines can be synthesized under relatively mild conditions by the reaction of 2-arylazirines with transition metal carbonyls. Coordinated nitrene species are probably intermediates in these reactions, and by careful selection of azirine ring substituents, such intermediates can undergo intramolecular ring closure leading to heterocyclic products (Scheme 89); an efficient synthesis of 1-aryl-3-phenylpyrazoles is illustrated in Scheme 90⁴⁷ and an analogous procedure leading to isoxazoles is described later (Scheme 109). It is interesting to note that the pyrazole products correspond to those formed in thermal rather than photochemical reactions of azirines,⁴⁹ hence molybdenum hexacarbonyl promotes C—N and not C—C bond cleavage.



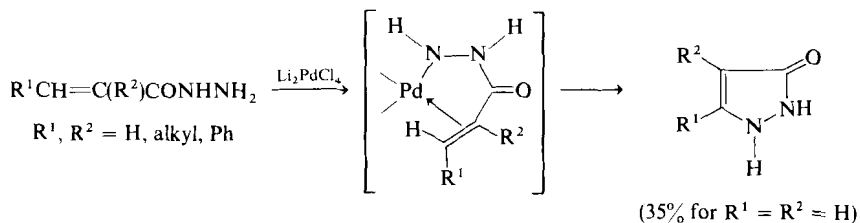
SCHEME 89



SCHEME 90

Pyrazolones have been prepared by palladium promoted cyclization of α,β -unsaturated carboxylic acid hydrazides but yields are only moderate (Scheme 91)¹⁵⁶ and no attempt has been made to effect a catalytic conversion.

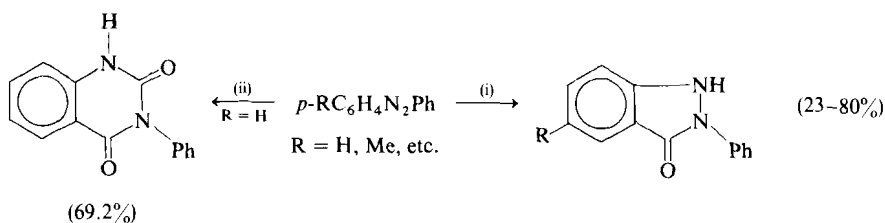
¹⁵⁶ A. Kasahara, *Chem. Ind. (London)*, 1032 (1976).



SCHEME 91

2. Indazoles

The dicobalt octacarbonyl-catalyzed transformation of azoarenes into 2-arylidiazolin-3-ones by carbonylation has been known for many years¹⁵⁷; high pressures of carbon monoxide are required and under more forcing conditions the products are quinazoline-2,4-diones (Scheme 92). Reactions

SCHEME 92. (i) $\text{Co}_2(\text{CO})_8$, CO, 180–190°C; (ii) as (i), but 220–230°C.

of this type probably involve the formation of an azoarene-cobalt complex followed by orthometallation⁹ and carbonyl insertion and it is significant that preformed orthopalladated complexes (cf. **74**) react with carbon monoxide to give indazolones^{158–160} in yields that are improved compared with the dicobalt octacarbonyl procedure (Scheme 93). A by-product in reactions of the latter type has also been isolated as a carbonylation product of the acetoxy-bridged palladium dimeric complex (**75**, Scheme 94).¹⁵⁹ This compound is a condensed indazolone derivative (**76**)¹⁶¹ and not a condensed lactone as has been erroneously formulated.^{157,159}

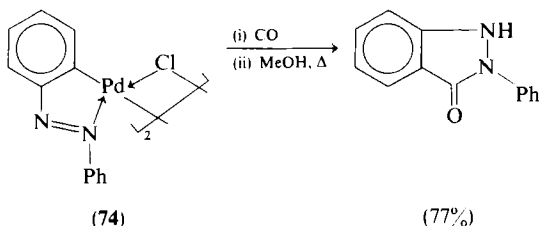
¹⁵⁷ S. Horie and S. Murahashi, *Bull. Chem. Soc. Jpn.* **33**, 88 (1960).

¹⁵⁸ S. Horie and S. Murahashi, *J. Am. Chem. Soc.* **78**, 4816 (1956).

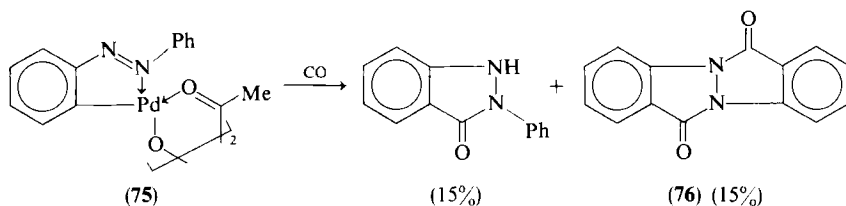
¹⁵⁹ J. M. Thompson and R. F. Heck, *J. Org. Chem.* **40**, 2667 (1975).

¹⁶⁰ Y. Yamamoto and H. Yamazaki, *Synthesis*, 750 (1976).

¹⁶¹ Cf. W. L. Mosby, *Chem. Ind. (London)*, 17 (1957).

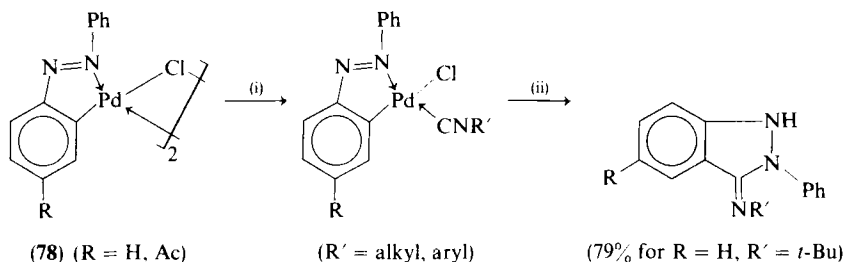


SCHEME 93



SCHEME 94

In reactions closely related to the carbonylation processes described above, the dimeric azoarene palladium complexes (78) can be transformed efficiently in two steps into 3-imino-2-phenylindazoles (Scheme 95).¹⁶²

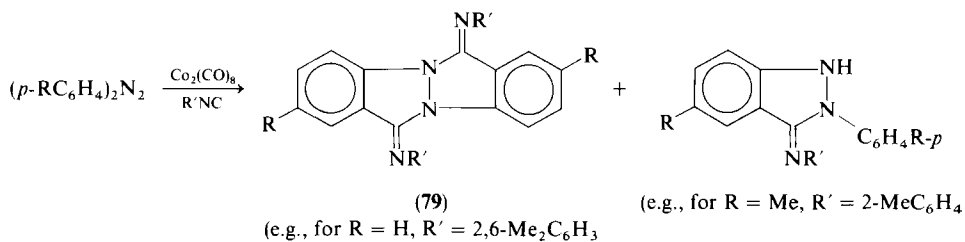


SCHEME 95. (i) R'NC, room temp. (ii) PhMe, 100–130°C.

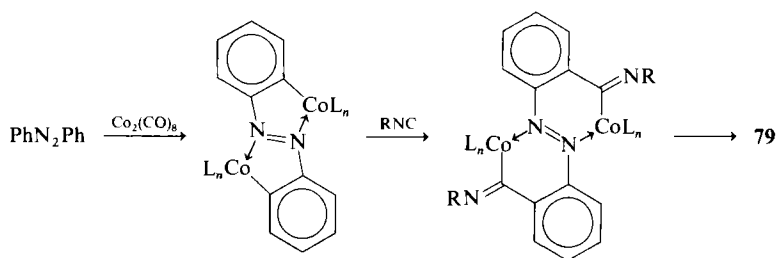
The indazole products can also be made directly from the palladium complexes 78 by heating them with the isonitrile in toluene at 120°C.¹⁶² They are also formed in dicobalt octacarbonyl-catalyzed reactions of azoarenes with isocyanides but in this case an alternative reaction pathway leading to indazolo[2,1-*a*]indazoles (79) is observed (Scheme 96).¹⁶³ Products of the latter type are formed from sterically hindered isocyanides hence it is likely that in these cases a double metallation is favored over isocyanide insertion into a monometallated species (Scheme 97).

¹⁶² Y. Yamamoto and H. Yamazaki, *Synthesis*, 750 (1976).

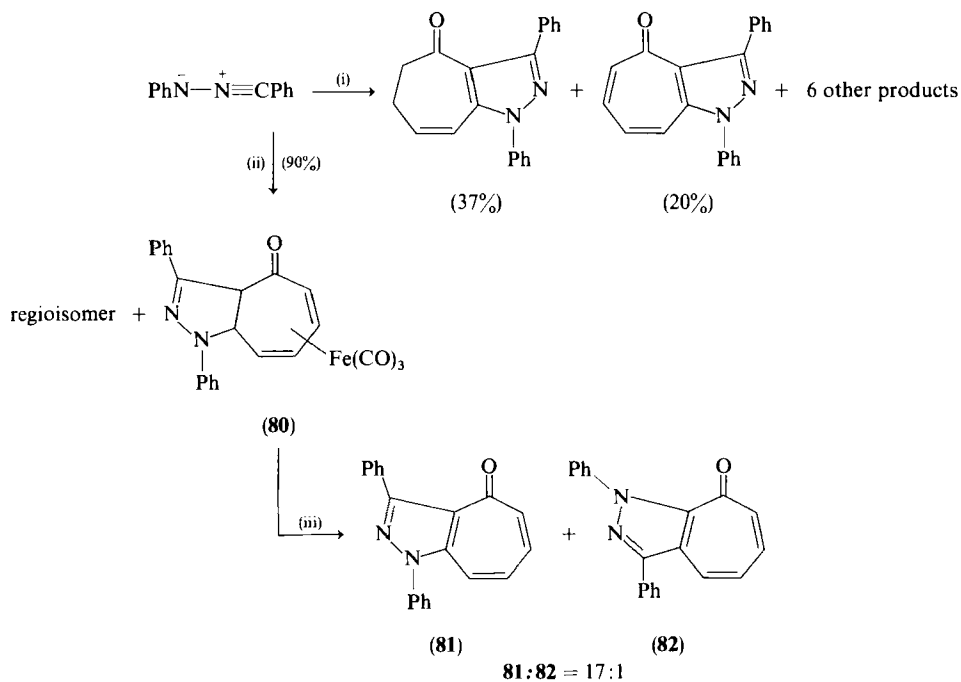
¹⁶³ Y. Yamamoto and H. Yamazaki, *J. Org. Chem.* **42**, 4136 (1977).



SCHEME 96



SCHEME 97



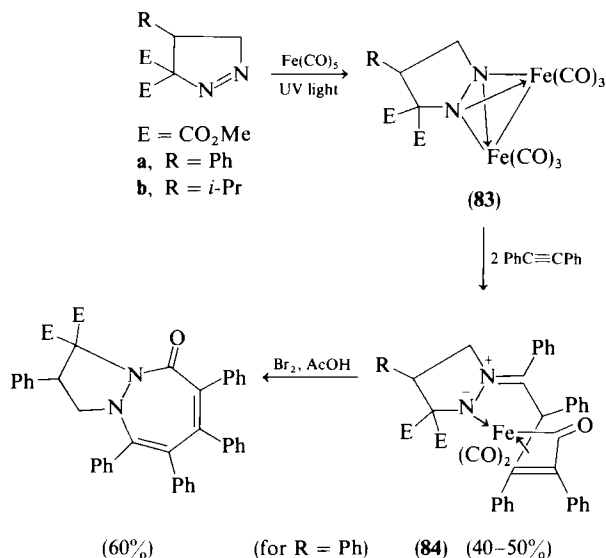
SCHEME 98. (i) Tropone, room temp.; (ii) tricarbonyltroponeiron; (iii) Ce^{IV}, Na₂HPO₄.

3. Cycloheptapyrazoles

In an uncatalyzed thermal process, diphenylnitrilimine reacts with tropone to give a complex mixture in which two cycloheptapyrazole derivatives predominate¹⁶⁴ (Scheme 98). In contrast, tricarbonyltroponeiron is converted in high yield into the iron complex **80** together with smaller quantities of its regioisomer; treatment of the product mixture with ceric ion effects deligation and oxidation to give the cycloheptapyrazole derivatives (**81**, **82**) in a ratio of 17:1 (Scheme 98). An important feature of this work is the regioselectivity achieved in the reaction of coordinated tropone, in which products arise by cycloaddition in the $[\pi 2s + \pi 4s]$ and not the $[\pi 6s + \pi 4s]$ mode.

4. Pyrazolodiazepins

The sequence illustrated in Scheme 99 provides an intriguing example of the manner in which a reactive diazene moiety in a metal complex (**83**) can be used in an annulation procedure.¹⁶⁵ The transformation **83** \rightarrow **84** involves a cyclooligomerization with concomitant carbonyl insertion, and ensuing



SCHEME 99

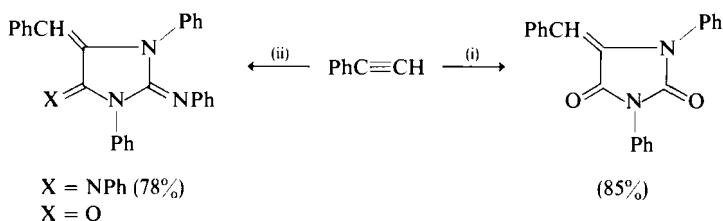
¹⁶⁴ M. Bonadeo, C. De Micheli, and R. Gandolfi, *J. C. S. Perkin I*, 939 (1977).

¹⁶⁵ B. Ulbrich and H. Kisch, *Angew. Chem., Int. Ed. Engl.* **17**, 369 (1978).

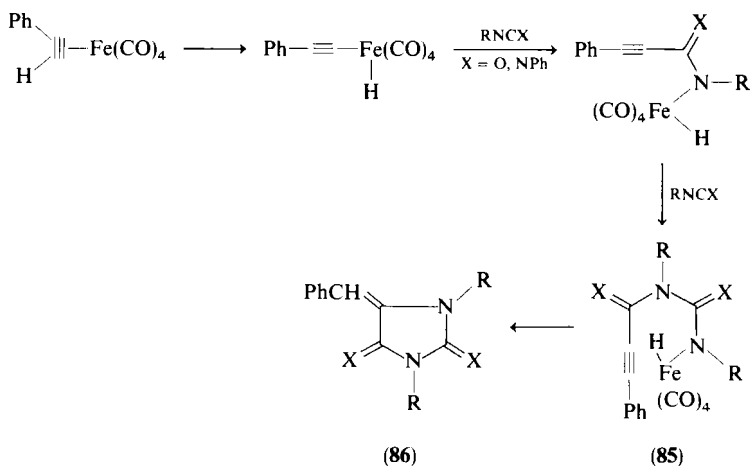
oxidative decomposition of the complex **83a** provides an unusual synthesis of the novel pyrazolodiazepin ring system. In principle it should be possible to elaborate upon this approach to effect the synthesis of a variety of heterocycles, although catalytic variants are obviously desirable.

5. Imidazoles

Good yields of imidazoline derivatives have been obtained in the co-cyclooligomerization of phenylacetylene with isocyanates and carbodiimides (Scheme 100).¹⁶⁶ It has been demonstrated¹⁶⁶ by labeling studies in the isocyanate reaction that the hydrogen shift is intramolecular and a mechanism accommodating this feature is illustrated in Scheme 101.¹⁶⁶ The final step (**85** → **86**) in the proposed¹⁶⁶ mechanism (Scheme 101) probably occurs via a coordinated acetylene complex and it is notable that related complexes



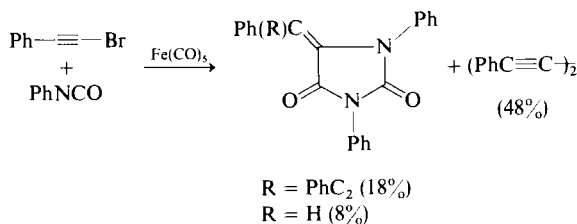
SCHEME 100. (i) PhNCO, Fe(CO)₅; (ii) PhNCNPh, Fe(CO)₅.



SCHEME 101

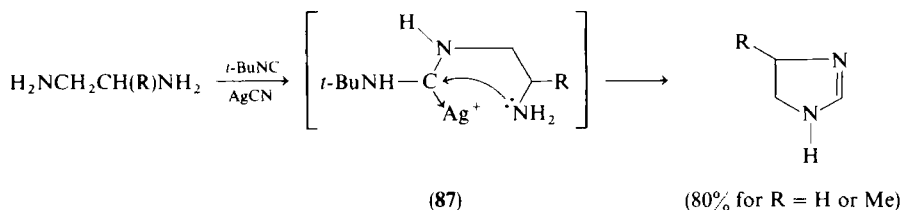
¹⁶⁶ Y. Oshiro, K. Kinugasa, T. Minami, and T. Agawa, *J. Org. Chem.* **35**, 2136 (1970).

are susceptible to nitrogen centered nucleophiles.¹⁶⁷ The use of phenyl-bromoacetylene has proved to be less useful in hydantoin synthesis (Scheme 102)¹⁶⁸ but this substrate reacts with diarylcarbodiimides and iron pentacarbonyl to give benzodiazepinones¹⁶⁸ (see Section VI,E).



SCHEME 102

Imidazolines are also formed in silver cyanide-catalyzed cyclization of alkyl isocyanides with aliphatic diamines (Scheme 103).¹⁶⁹ This simple synthesis can be applied in a general way with difunctional nucleophiles and has been used to prepare benzimidazoles, oxazoles, thiazoles, and oxazines.¹⁶⁹ It is suggested that transient carbene complexes are formed in these reactions (cf. **87** in Scheme 103) but further work is required to ascertain the mechanism and scope of these processes.



SCHEME 103

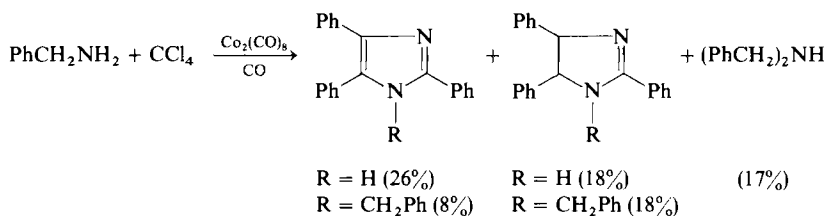
A direct synthesis of triarylhydrazoles and triarylhydrazolines has been accomplished by the dicobalt octacarbonyl-catalyzed reaction of benzylamine derivatives with carbon tetrachloride. When the reaction temperature is 150°C a complex product is formed and yields of heterocyclic products are poor. By lowering the reaction temperature to 120°C or reducing the reaction time, or by using $[\text{Mo}(\text{CO})_6]$ and $[\eta^5\text{-C}_5\text{H}_5\text{Mo}(\text{CO})_3]_2$ as the

¹⁶⁷ A. J. Carty, G. N. Mott, N. J. Taylor, and J. E. Yule, *J. Am. Chem. Soc.* **100**, 3051 (1978).

¹⁶⁸ A. Baba, Y. Oshiro, and T. Agawa, *J. Organomet. Chem.* **87**, 247 (1975).

¹⁶⁹ Y. Ito, Y. Inubushi, M. Zenbayashi, S. Tomita, and T. Saegusa, *J. Am. Chem. Soc.* **95**, 4447 (1973).

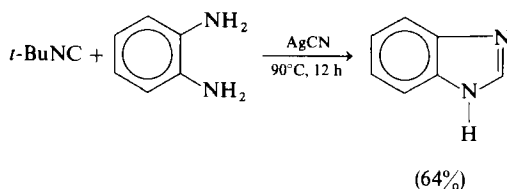
catalyst, a greater degree of selectivity can be achieved (Scheme 104).¹⁷⁰ The mechanism of processes of this type is obscure and the suggestion¹⁷⁰ that the reactions are free radical in character remains unsubstantiated.



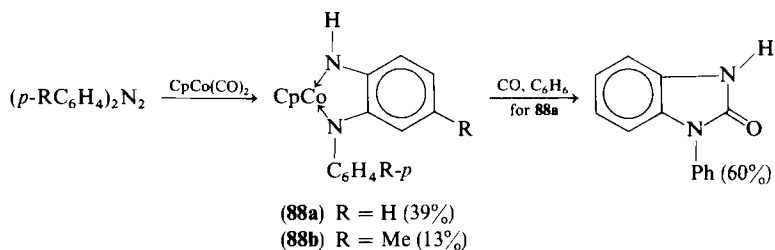
SCHEME 104

6. Benzimidazoles

The scope of the silver cyanide-catalyzed reaction of difunctional nucleophiles with alkyl isocyanides has been described in the earlier section on imidazoles; an example of the use of this simple approach in benzimidazole synthesis is illustrated in Scheme 105.¹⁶⁹



SCHEME 105



SCHEME 106

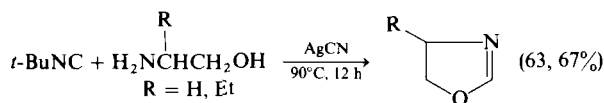
¹⁷⁰ Y. Mori and J. Tsuji, *Tetrahedron*, 4039 (1971); Japanese Patent 73/37032 [*CA* **81**, 3935 (1974)].

Subtle differences in the behavior of azoarenes toward cobalt carbonyl derivatives are observed in regard to metal-complex formation. Azobenzene is transformed by dicobalt octacarbonyl in processes of orthometallation and carbonyl insertion into 2-phenylindazolin-3-one (see Section IV,D,2). In contrast, cyclopentadienylcobalt dicarbonyl effects N—N bond cleavage, and carbonylation of the isolable complex **88a** provides 1-phenylbenzimidazolin-2-one (Scheme 106).¹⁷¹

E. WITH TWO HETEROATOMS (N,O)

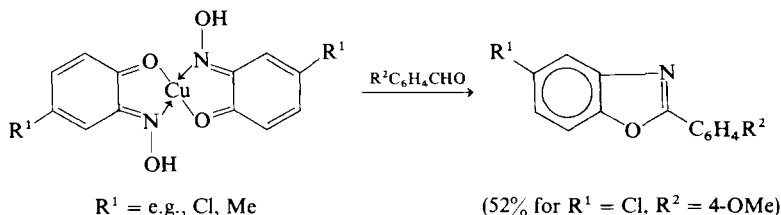
1. Oxazoles and Benzoxazoles

The reaction of difunctional nucleophiles with alkyl isocyanides under the influence of silver cyanide as catalyst has been described in an earlier section on imidazoles; an example of the use of this simple approach in an oxazoline synthesis is shown in Scheme 107.¹⁶⁹



SCHEME 107

2-Arylbenzoxazoles have been prepared in moderate yields by allowing aromatic aldehydes to react with copper complexes of *o*-nitrosophenols (Scheme 108).¹⁷² The role of the copper in reactions of this type is unclear but it may be noted that the uncomplexed nitrosophenols are relatively labile.¹⁷³ Copper complexes of *o*-nitrosophenols have also been used for the synthesis of benzoxazines (see Section V,D).



SCHEME 108

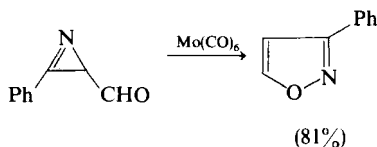
¹⁷¹ T. Joh, N. Hagihara, and S. Murahashi, *Bull. Chem. Soc. Jpn.* **40**, 661 (1967).

¹⁷² E. Yu Belyaev, M. S. Tovbis, T. P. Kononchuk, and A. V. El'tsov, *Khim. Geterotsikl. Soedin.*, 1338 (1976) [*Engl. Transl.*, 1109 (1976)].

¹⁷³ G. Cronheim, *J. Org. Chem.* **12**, 1 (1947).

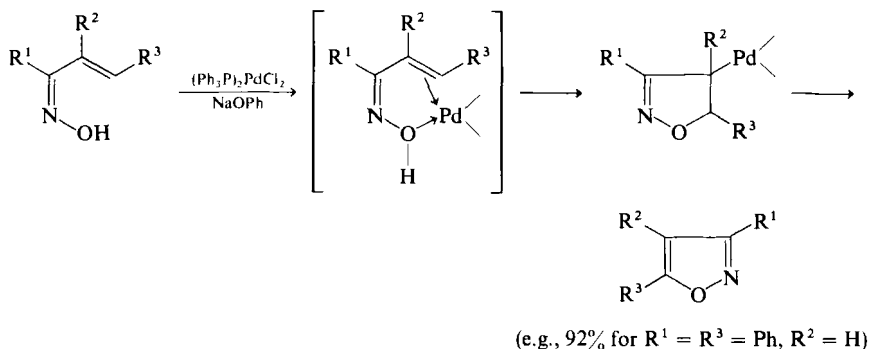
2. Isoxazoles

The formation of pyrazoles from reactions of suitably substituted 2-arylazirines and molybdenum hexacarbonyl has been discussed earlier in this section (see Schemes 89, 90)⁴⁷; an analogous procedure depicting the transformation of 2-formyl-3-phenyl-2*H*-azirine into 3-phenylisoxazole is illustrated in Scheme 109.⁴⁷



SCHEME 109

Isoxazole derivatives have also been synthesized in variable yield by the palladium-catalyzed intramolecular oxidative cyclization of α,β -unsaturated oximes (Scheme 110).¹⁷⁴ Reactions of this type are reminiscent of procedures



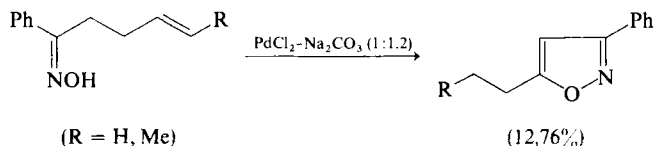
SCHEME 110

devised for the synthesis of benzofurans from *o*-allylphenols (See Scheme 70 in Section IV,B,4). γ,δ -Unsaturated oximes are also transformed by $\text{PdCl}_2\text{--Na}_2\text{CO}_3$ (1:1.2) in methylene chloride, presumably by an initial step of double-bond isomerization, into isoxazoles (see Scheme 111) but when dichlorobis(triphenylphosphine)palladium is used as the catalyst, the products are pyridine derivatives (see Scheme 136 in Section V,A,1).¹⁷⁵

Aliphatic aldoximes and ketoximes undergo palladium-catalyzed O- and N-alkylation by butadiene in reactions that presumably occur via π -allyl

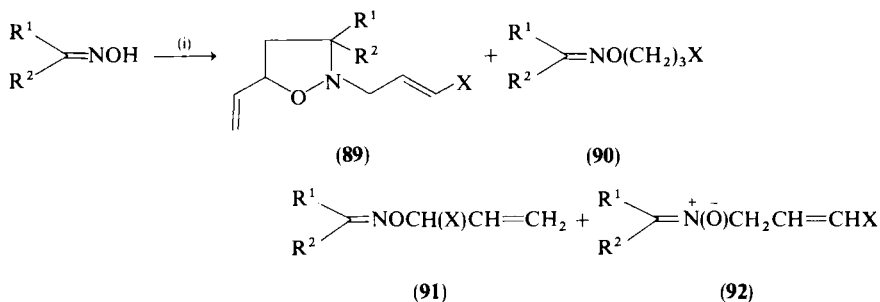
¹⁷⁴ K. Maeda, T. Hosokawa, S. Murahashi, and I. Moritani, *Tetrahedron Lett.*, 5075 (1973).

¹⁷⁵ T. Hosokawa, N. Shimo, K. Maeda, A. Sonoda, and S. Murahashi, *Tetrahedron Lett.*, 383 (1976).



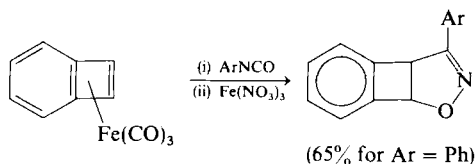
SCHEME 111

intermediates (Scheme 112).¹⁷⁶ The isoxazolidine products probably arise from 1,3-dipolar cycloaddition reactions of intermediate nitrones (cf. **92**) and in this context it is noteworthy that such intermediates can be diverted in competing reactions with ethylene.¹⁷⁶

SCHEME 112. (i) $\text{Pd}(\text{NO}_3)_2 \cdot 4\text{Ph}_3\text{P}$, C_4H_6 ; $\text{X} = \text{CH}_2=\text{CH}(\text{CH}_2)_3$.

3. 3a,7b-3-Arylbenzo[3,4]cyclobuta[1,2-d]isoxazoles

Benzocyclobutene, when generated by oxidation of its iron tricarbonyl complex, can function as the dipolarophile in 1,3-dipolar cycloaddition reactions with arynitrile oxides (Scheme 113).¹⁷⁷ Unfortunately the synthetic versatility of this type of process is limited because of the unreactivity of other 1,3-dipolar species such as phenyl azide, benzonitrile *N*-phenylimide, and α -(*p*-tolyl)benzylidenamine *N*-oxide.¹⁷⁷



SCHEME 113

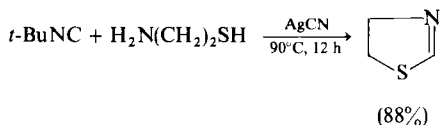
¹⁷⁶ R. Baker and M. S. Nobbs, *Tetrahedron Lett.*, 3759 (1977).

¹⁷⁷ T. L. Gilchrist, E. E. Nunn, and C. W. Rees, *J. C. S. Perkin I*, 1262 (1974).

F. WITH TWO HETEROATOMS (N,S)

1. *Thiazoles and Benzothiazoles*

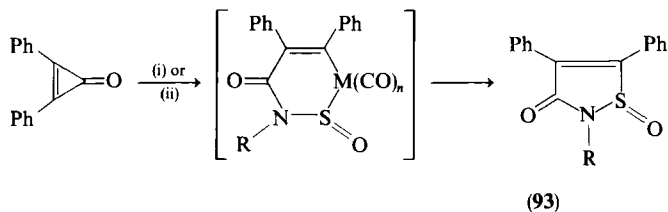
The reaction of difunctional nucleophiles with alkyl isocyanides has been described in an earlier section on imidazoles; an example of the use of this simple approach in thiazole synthesis is illustrated in Scheme 114.¹⁶⁹



SCHEME 114

2. *Isothiazoles*

The formation of 1,3,4-triarylpyrroline-2,5-diones from the reaction of diphenylcyclopropenone and *N*-sulfinylarylamines with nickel carbonyl has been described earlier (see Scheme 36 in Section IV,A,2).⁶⁴ In contrast with this result, 2,4,5-triphenyl-3-isothiazolone 1-oxide is produced in this type of process using iron pentacarbonyl, and the analogous cyclohexyl derivative is formed in a nickel carbonyl-mediated reaction (Scheme 115).⁶⁴ It is probable that metallocyclic species (cf. **93**) are intermediates in these transformations.

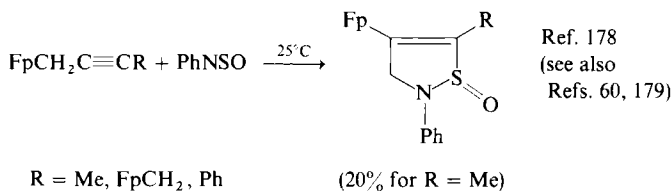


SCHEME 115. (i) PhNSO₂, Fe(CO)₅, [gives R = Ph (21%)]; (ii) C₆H₁₁NSO₂, Ni(CO)₄, gives R = C₆H₁₁ (36%).

The mechanism and synthetic scope of the reactions of *monohaptoallyl*- and *-propargyliron* complexes have been described earlier (see Schemes 30–33 in Section IV,A,2).⁶¹ An example of the synthesis of isothiazolines is given in Scheme 116.¹⁷⁸ Unfortunately, yields are either low or unspec-

¹⁷⁸ P. W. Robinson and A. Wojcicki, *Chem. Commun.*, 951 (1970).

¹⁷⁹ S. Raghu and M. Rosenblum, *J. Am. Chem. Soc.* **95**, 3060 (1973).

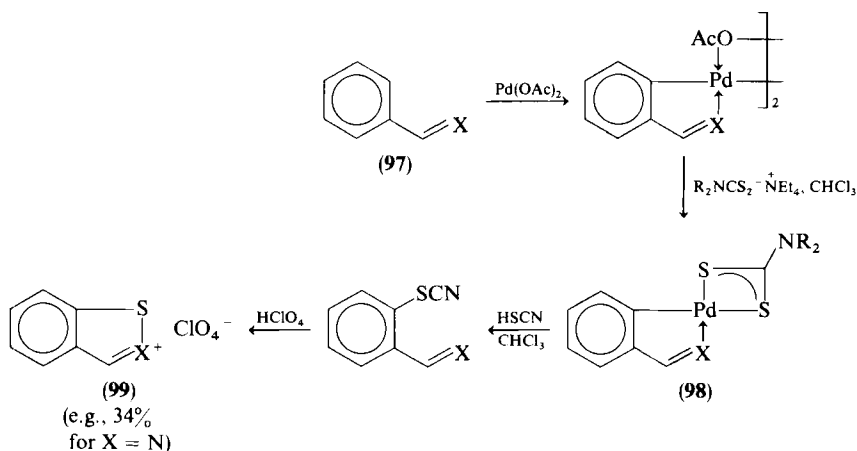


SCHEME 116

ified, and no attempt has been made to prepare the parent heterocycles from the organoiron products (cf. an earlier successful method for iron-substituted pyrrolidones).⁶⁰

3. Condensed Isothiazolium Compounds

The conversion of functionalized arenes as represented by the general formula **97**, into isothiazolium compounds (**99**) has been achieved by the sequence shown in Scheme 117.¹⁸⁰ From a synthetic viewpoint, transformation of cyclopalladated products into thiocyanate derivatives is more efficiently achieved using monomeric dithiocarbamate complexes (**98**) rather than dimeric compounds. The generation of analogous dithiolylium perchlorates by a related procedure is described later (see Section IV,H).



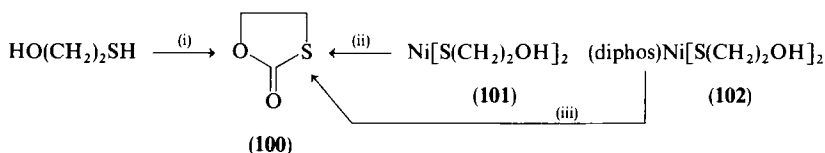
SCHEME 117

¹⁸⁰ R. C. Davis, T. J. Grinter, D. Leaver, and R. M. O'Neil, *Tetrahedron Lett.*, 3339 (1979).

G. WITH TWO HETEROATOMS (O,S)

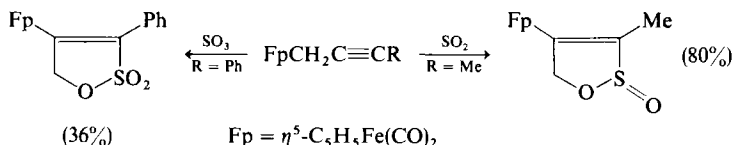
Oxathioles

A 1,3-oxathiolane derivative (**100**) is formed when 2-mercaptoethanol is carbonylated by nickel carbonyl in pyridine (Scheme 118).¹⁸¹ It is probable that the mechanism involves carbonyl insertion into the Ni—S bond of intermediate thiolatonickel complexes and it is significant that compounds in this category (cf. **101**, **102**) can be transformed into the cyclic thiocarbonate by treatment with carbon monoxide (Scheme 118).¹⁸¹



SCHEME 118. (i) Ni(CO)₄, CO, pyridine; (ii) CO, pyridine; (iii) CO, Cl(CH₂)₂Cl.

The mechanism and synthetic scope of reactions of monohaptopropargyl-iron complexes has been described earlier (see Schemes 30–33 in Section IV,A,2). By using sulfur dioxide and sulfur trioxide as electrophilic reagents, it is possible to synthesize metal-containing heterocycles in the reduced 1,2-oxathiole category (sultines and sultones) (Scheme 119).^{182–184} An



SCHEME 119

iron-substituted 1,2-oxathiolane 2-oxide has also been synthesized by metal-assisted ring opening of a monohaptocyclopropyliron complex (Scheme 120),¹⁸⁵ but no attempt has been made to convert the organometallic products shown in Schemes 119 and 120 into the unsubstituted parent heterocycles.

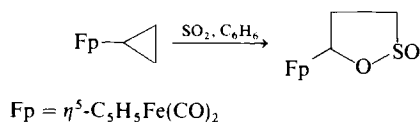
¹⁸¹ P. Koch and E. Perrotti, *J. Organomet. Chem.* **81**, 111 (1974).

¹⁸² W. D. Bannister, B. L. Booth, R. N. Haszeldine, and P. L. Loader, *J. Chem. Soc. A*, 930 (1971).

¹⁸³ J. E. Thomasson, P. W. Robinson, D. A. Ross, and A. Wojcicki, *Inorg. Chem.* **10**, 2130 (1971).

¹⁸⁴ D. W. Lichtenberg and A. Wojcicki, *Inorg. Chim. Acta* **7**, 311 (1973).

¹⁸⁵ A. Cutler, R. W. Fish, W. P. Giering, and M. Rosenblum, *J. Am. Chem. Soc.* **94**, 4354 (1972).

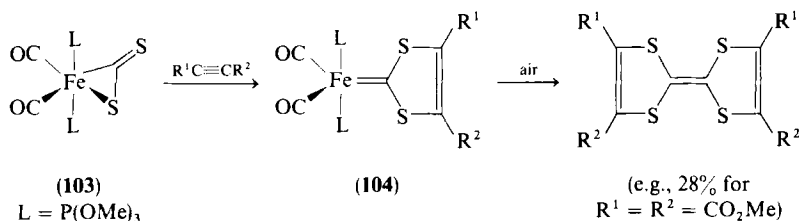


SCHEME 120

H. WITH TWO HETEROATOMS (S,S)

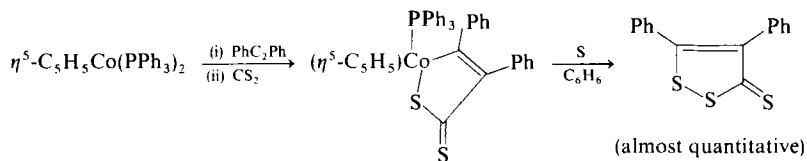
1. Dithioles

In contrast to the reaction of an $\eta^2\text{-CS}_2$ -rhodium complex with dimethyl acetylenedicarboxylate which gives rise to a metallocycle,¹⁸⁶ the iron complexes **103** are converted by activated acetylenes into air-sensitive carbene complexes **104**. Decomposition of the latter in air provides an unusual synthetic route to substituted tetrathiofulvene derivatives (Scheme 121).¹⁸⁷



SCHEME 121

A closely related route to a monocyclic dithiole derivative is shown in Scheme 122.¹⁸⁶ The easy replacement of cobalt by sulfur in this type of process has analogy in the synthesis of a variety of condensed heterocycles from rhodacyclopentadienes (see Scheme 127 in Section IV,H,1) and cobaltacyclopentadienes (see Scheme 82 in Section IV,C,1).



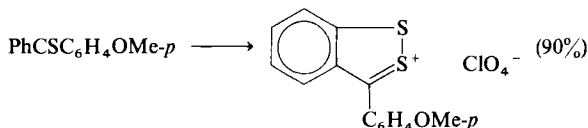
SCHEME 122

¹⁸⁶ Y. Wakatsuki, H. Yamazaki, and H. Iwasaki, *J. Am. Chem. Soc.* **95**, 5781 (1973).

¹⁸⁷ H. LeBozec, A. Gorgues, and P. Dixneuf, *J. Am. Chem. Soc.* **100**, 3946 (1978); see also *J. C. S. Chem. Commun.*, 573 (1978).

2. 1,2-Dithiolylum Salts

An orthometallation procedure for the preparation of condensed isothiazolium salts from appropriately substituted arenes has been described earlier in this Section (Scheme 117)¹⁸⁰; an example illustrating the way in which this approach can be elaborated to the synthesis of condensed 1,2-dithiolylum perchlorates is given in Scheme 123.

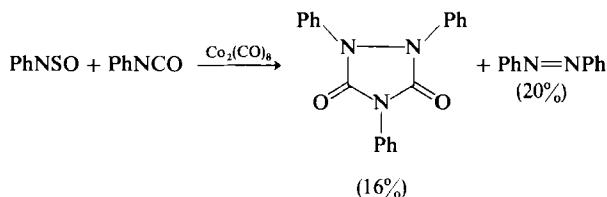


SCHEME 123

I. WITH THREE HETEROATOMS

1. Triazoles and Condensed Derivatives

In contrast to thermal uncatalyzed reactions of *N*-acylsulfinylamines with aryl isocyanates which give rise to azoarenes,¹⁸⁸ the cobalt or iron carbonyl-catalyzed process gives additionally 3,5-dioxo-1,2,4-triphenyl-1,2,4-triazolidine (Scheme 124).¹⁸⁹ The only possible restriction on this simple urazole synthesis would be the expectation that the substituents on the reactants must be the same to prohibit exchange.



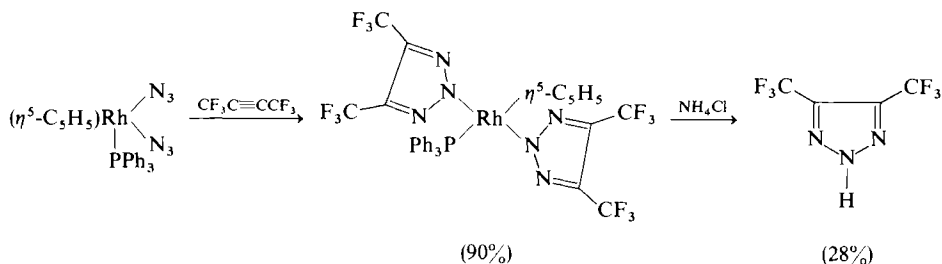
SCHEME 124

Azidorhodium complexes are of considerable structural interest, but limited applicability can be expected from the unusual triazole synthesis illustrated in Scheme 125.¹⁹⁰ It is also difficult to envisage synthetic utility from reactions in which organic azides are decomposed by transition metal carbonyls. Thus 2-arylbenzotriazoles are formed in such reactions on

¹⁸⁸ T. Minami, H. Miki, and T. Agawa, *Kogyo Kagaku Zasshi* **70**, 1831 (1967).

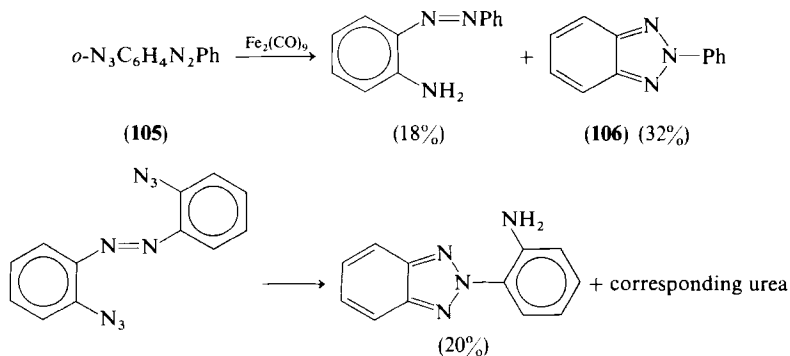
¹⁸⁹ T. Drapier, A. J. Hubert, and P. Teyssié, *Synthesis*, 649 (1975).

¹⁹⁰ W. Rigby, P. M. Bailey, J. A. McLeverty, and P. M. Maitlis, *J. C. S. Dalton*, 371 (1979).



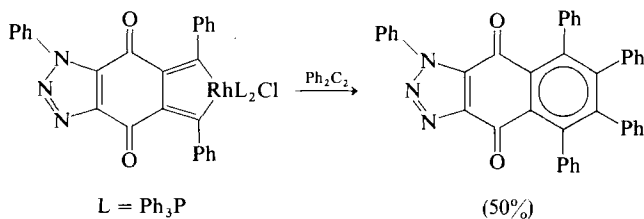
SCHEME 125

2-azidoazoarenes (Scheme 126)¹⁹¹ but conversions of this type (e.g., **105** → **106**) can be effected quantitatively in uncatalyzed thermal processes at 80°C



SCHEME 126

The preparation of condensed rhodacyclopentadienes via the diyne reaction, and examples of their use in heterocyclic synthesis have been described earlier (see Schemes 79 and 86 in Sections IV,B,5 and IV,C,2). An example showing the application of this approach to the synthesis of a condensed triazole is shown in Scheme 127.¹⁹²



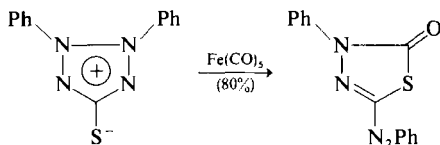
SCHEME 127

¹⁹¹ C. D. Campbell and C. W. Rees, *Chem. Commun.*, 537 (1969).

¹⁹² E. Müller and W. Winter, *Justus Liebigs Ann. Chem.*, 1876 (1974).

2. Thiadiazoles

The mesoionic tetrazole dehydrodithizone is transformed by iron pentacarbonyl into 4-phenyl-2-phenylazo- Δ^2 -1,3,4-thiadiazolin-5-one, presumably by a mechanism of ring opening, complexation, carbonyl insertion and subsequent ring closure (Scheme 128).¹⁹³ Unfortunately, analogous processes do not occur on other mesoionic compounds in the 1,2,3-oxadiazole, *s*-triazole or tetrazole series, and the scope of this unusual carbonylation is probably limited.



SCHEME 128

V. Six-Membered Ring Compounds

A. WITH NITROGEN AS HETEROATOM

1. Pyridines

Transition metal complexes have been used in a number of reactions leading to the direct synthesis of pyridine derivatives from acyclic compounds and from other heterocycles. It is pertinent also to describe two methods that have been employed to prepare difficultly accessible 3-alkyl-, 3-formyl-, and 3-acylpyridines. By elaborating on reported^{194,195} procedures used in aromatic reactions, it is possible to convert 3-bromopyridines to products containing a 3-oxoalkyl function¹⁹⁶ (Scheme 129). A minor problem in this simple catalytic process is caused by the formation in some cases of 2-substituted pyridines but this is minimized by using dimethylformamide as the solvent.¹⁹⁶

Carbonylation at the 3-position of a pyridine is illustrated in Scheme 130.¹⁹⁷ In these processes the intermediate carbanion from arylation of pyridine can be trapped by iron pentacarbonyl and the ensuing acyliron

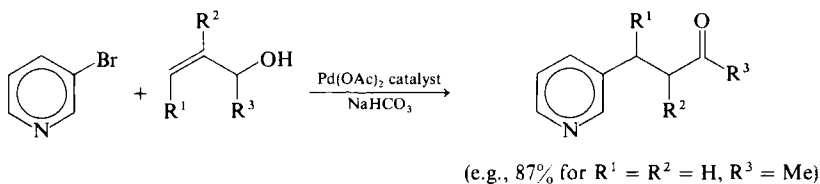
¹⁹³ P. N. Preston, N. J. Robinson, K. Turnbull, and T. J. King, *J. C. S. Chem. Commun.*, 998 (1974); P. N. Preston and K. Turnbull, *J. C. S. Perkin II*, 1229 (1977).

¹⁹⁴ J. B. Melpolder and R. F. Heck, *J. Org. Chem.* **41**, 265 (1976).

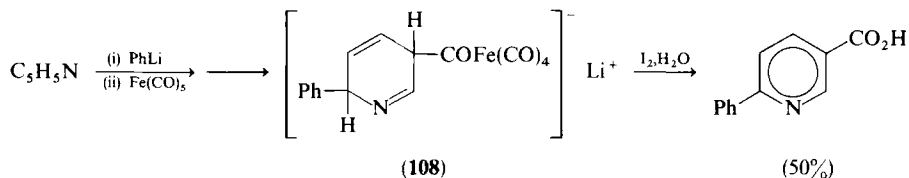
¹⁹⁵ A. J. Chalk and S. A. Magennis, *J. Org. Chem.* **41**, 273, 1206 (1976).

¹⁹⁶ Y. Tamaru, Y. Yamada, and Z. Yoshida, *J. Org. Chem.* **43**, 3396 (1978).

¹⁹⁷ C. Giam and K. Ueno, *J. Am. Chem. Soc.* **99**, 3166 (1977).



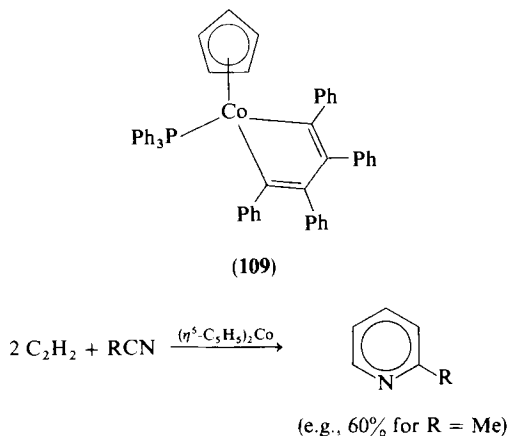
SCHEME 129



SCHEME 130

species (108) from carbonyl insertion can be decomposed in conventional reactions leading to 2-phenylpyridine-5-carboxylic acid and related compounds. A wider study of this approach in heterocyclic synthesis would be desirable.

Direct pyridine syntheses by the cocyclooligomerization of one molecule of a nitrile and 2 molecules of an acetylene can be achieved catalytically by cobalt(I) species prepared *in situ*¹⁹⁸ or by the cobaltacyclopentadiene derivative 109. The latter compound is a good catalyst but can be trouble-

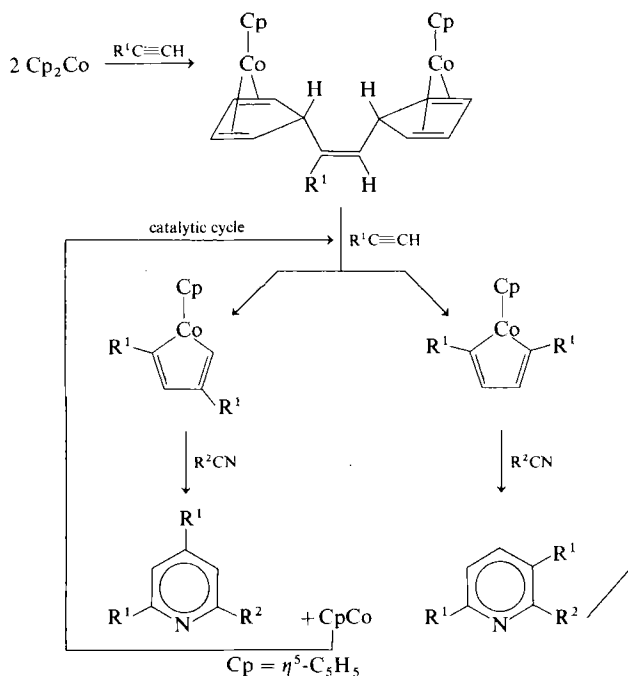


SCHEME 131

¹⁹⁸ H. Bönemann, R. Brinkmann, and H. Schenkluhn, *Synthesis*, 575 (1974); see also H. Bönemann, *Angew. Chem., Int. Ed. Engl.* **17**, 505 (1978).

some to prepare¹⁹⁹ and it is advantageous to use cobaltocene (di- η^5 -cyclopentadienylcobalt).²⁰⁰ An example of this direct synthesis is shown in Scheme 131 and the proposed²⁰⁰ mechanism incorporating a catalytic cycle is depicted in Scheme 132. A related process leading to pyridine derivatives with a more complex substitution pattern is given in Scheme 133²⁰¹ and elaboration of the method to the syntheses of isoquinolines and related compounds is described later in this section (see Scheme 148).

Pyrrolidone is the major product when allylamine is subjected to the conditions of the oxo process using dicobalt octacarbonyl as the catalyst.²⁰³ The by-products are pyridine derivatives **112** and **113** and these compounds become the major products when iron pentacarbonyl is used as the catalyst;



SCHEME 132

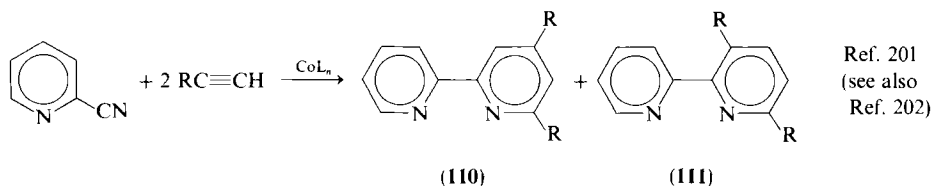
¹⁹⁹ Y. Wakatsuki, T. Kuramitsu, and H. Yamazaki, *Tetrahedron Lett.*, 4549 (1974); H. Yamazaki and N. Hagihara, *Bull. Chem. Soc. Jpn.*, **44**, 2260 (1971).

²⁰⁰ Y. Wakatsuki and H. Yamazaki, *Synthesis*, 26 (1976).

²⁰¹ H. Bönemann and R. Brinkmann, *Synthesis*, 600 (1975).

²⁰² K. P. C. Vollhardt and R. G. Bergman, *J. Am. Chem. Soc.*, **96**, 4996 (1974).

²⁰³ J. Falbe and F. Korte, *Tetrahedron Lett.*, 2677 (1965).



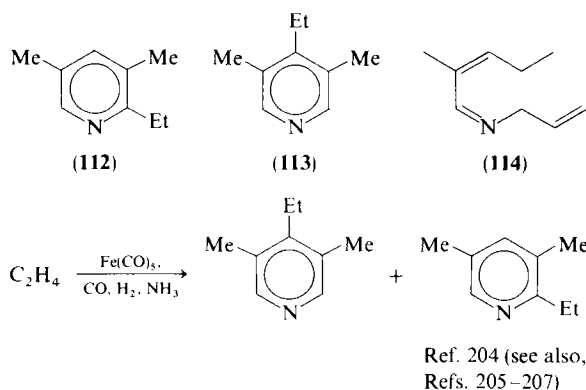
Cp = $\eta^5\text{-C}_5\text{H}_5$
 CoL_n = Cyclopentadienyl-
 1,5-cyclooctadienylcobalt

| R | Yield (%) | Ratio 110:111 |
|----|-----------|---------------|
| H | 95 | — |
| Me | 91 | 72:28 |
| Ph | 79 | 69:31 |

SCHEME 133

significantly, the imino derivative **114** can be isolated when the latter reaction is carried out at 160°C and this compound can be transformed in a separate thermal reaction at 250°C into the pyridine derivative **112**.²⁰³ The pyridine precursor **114** may arise from the condensation of allylamine with propionaldimine, and other reactions that can generate such an intermediate also give rise to the formation of pyridine derivatives (see Scheme 135).

β,γ -Unsaturated ketoximes are transformed by stoichiometric amounts of palladium chloride–sodium carbonate in methylene chloride into isoxazole



SCHEME 135

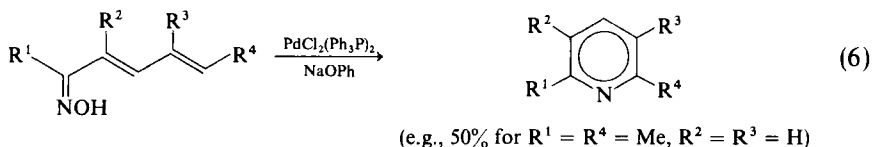
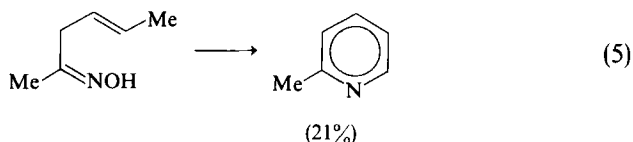
²⁰⁴ A. Striegler and J. Weber, *J. Prakt. Chem.* **29**, 281 (1965).

²⁰⁵ J. Falbe and F. Korte, *Brennstoffchemie* **46**, 276 (1965).

²⁰⁶ A. G. Mohan, *J. Org. Chem.* **35**, 3982 (1970).

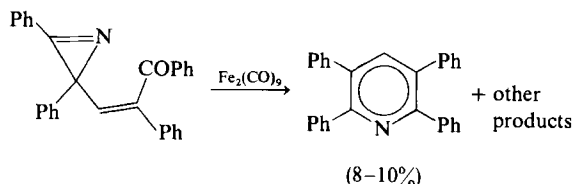
²⁰⁷ J. Kiji, S. Nishimura, K. Yamamoto, and J. Furukawa, *Bull. Chem. Soc. Jpn.* **48**, 3417 (1975).

derivatives (see Scheme 111 in Section IV,E,2),²⁰⁸ but by using a different reaction medium [$\text{PdCl}_2(\text{Ph}_3\text{P})_2$, NaOPh , C_6H_6], the products are pyridine derivatives.²⁰⁸ (Scheme 136, Eq. 5). The products must arise by a mechanism including double bond isomerization, and a similar type of reaction occurs with γ,δ -unsaturated ketoximes. Pyridine formation in the latter case must involve an additional step of dehydrogenation at the α,β -position, and it is significant that better yields of alkylpyridines can be isolated from analogous reactions of the oximes of appropriate dienones (Scheme 136, Eq. 6). It is notable that oximes of the latter type are converted in thermal reactions at 300°C into alkylpyridines²⁰⁹ hence the palladium-promoted procedure offers a valuable alternative route, albeit that stoichiometric quantities of palladium are necessary.



SCHEME 136

Pyrrole derivatives are the major products formed from treatment of Z-ketovinylazirines with enneacarbonyldiiron (see Scheme 23 in Section IV,A,1).⁵⁰ 2,3,5,6-Tetraphenylpyridine is also formed but in very low yield, and little synthetic application can be anticipated for this type of process (Scheme 137).



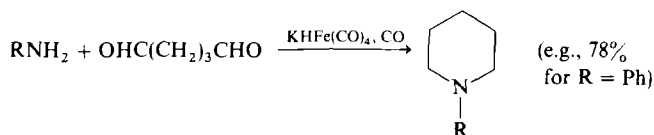
SCHEME 137

²⁰⁸ T. Hosokawa, N. Shimo, K. Maeda, A. Sonada, and S. Murahashi, *Tetrahedron Lett.*, 383 (1976).

²⁰⁹ See M. Scholtz and W. Meyer, *Ber. Dtsch. Chem. Ges.* **43**, 1861 (1910), and references cited therein.

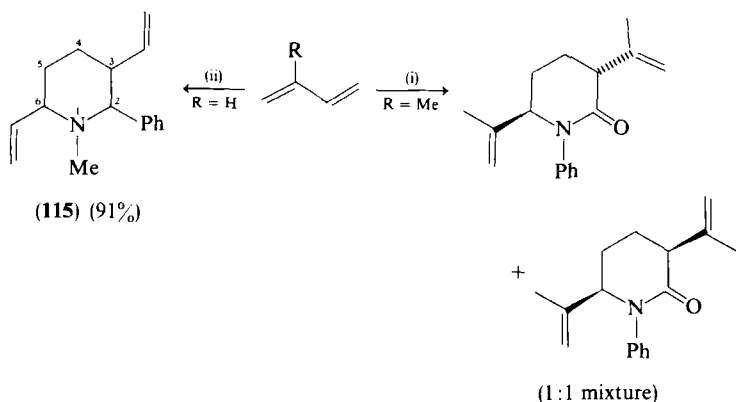
2. Piperidines

The excellent reducing properties of potassium tetracarbonylhydride-ferrate have been used to good effect in providing an efficient general piperidine synthesis from alkyl and aryl amines and glutaraldehyde²¹⁰ (Scheme 138). The reaction probably proceeds via reduction of intermediate Schiff bases and cyclization via the iminium salt.



SCHEME 138

π -Allyl complexes are presumably the intermediates in synthetic methods leading to tetrasubstituted piperidine derivatives from palladium-catalyzed reactions of 1,3-dienes with phenyl isocyanate²¹¹ or a Schiff base²¹² (Scheme 139). Yields are high, but in both types of process isomer mixtures are formed; it is notable that the four-component mixture of *N*-methylpiperidines (**115**) can be isomerized catalytically by $\text{Pd}(\text{NO}_3)_2\text{-Ph}_3\text{P}$ at 80°C in a process which may involve an intermediate π -allyl species formed by N-C-6 bond fission.



SCHEME 139. (i) $(\text{Ph}_3\text{P})_2(\text{maleic anhydride})\text{Pd} + \text{PhNCO}$; (ii) $\text{Pd}(\text{NO}_3)_2\text{:Ph}_3\text{P}$ (1:3) + PhCHNMe .

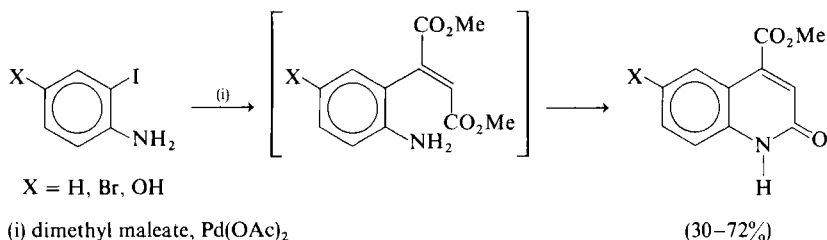
²¹⁰ Y. Watanabe, S. C. Shim, T. Mitsudo, M. Yamashita, and Y. Takegami, *Bull. Chem. Soc. Jpn.* **49**, 2302 (1976).

²¹¹ K. Ohno and J. Tsuji, *Chem. Commun.*, 247 (1971).

²¹² J. Kiji, K. Yamamoto, H. Tomita, and J. Furukawa, *J. C. S. Chem. Commun.*, 506 (1974).

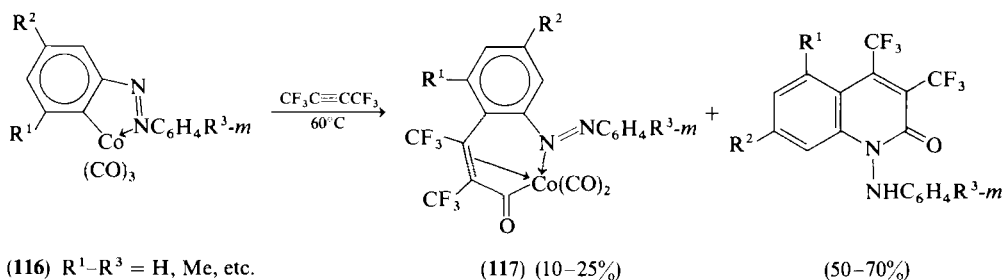
3. Quinolines

The palladium-catalyzed arylation of alkenes by haloarenes, and applications in furan synthesis have been described earlier (see Eq. 14 in Section IV,B,1). By employing *o*-aminoiodoarenes and appropriately substituted (*Z*)-alkenes it has proved possible to develop an efficient synthetic route to quinolin-2-ones (Scheme 140).²¹³



SCHEME 140

Good yields of 1-arylaminquinolin-2-ones are obtained when the azo-arene complexes **116** are treated with hexafluorobut-2-yne (Scheme 141).²¹⁴ This procedure is particularly novel in the chemistry of orthometallated complexes in that the primary organometallic products (**117**) arise from the formal insertion of a three carbon unit [CO + C₂(CF₃)₂] into the aryl-cobalt bond of **116**. A wider study of the scope of this type of process using a variety of orthometallated complexes would be desirable.

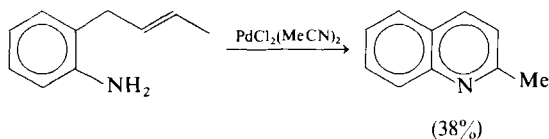


SCHEME 141

In general, palladium-catalyzed reactions of 2-allylarylamines lead to the formation of 2-alkylindoles (see Scheme 48 in Section IV,A,3).⁷⁶ The stoichiometric reaction illustrated in Scheme 142 also occurs catalytically

²¹³ N. A. Cortese, C. B. Ziegler, B. J. Hrnjez, and R. F. Heck, *J. Org. Chem.* **43**, 2952 (1978).

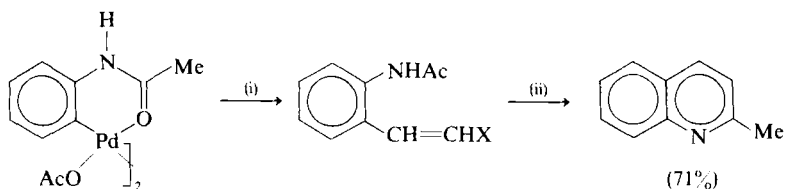
²¹⁴ M. I. Bruce, B. L. Goodall, A. D. Redhouse, and F. G. A. Stone, *J. C. S. Chem. Commun.*, 1228 (1972); M. I. Bruce, B. L. Goodall, and F. G. A. Stone, *J. C. S. Dalton*, 1651 (1975).



SCHEME 142

using Cu^{2+} or benzoquinone to reoxidize $\text{Pd}(0)$ to $\text{Pd}(\text{II})$. However, when excess benzoquinone or lithium chloride is added to the standard catalytic system, 2-crotylaniline is converted in the alternative cyclization mode into 2-ethylindole.⁷⁶ This subtle effect on the regioselectivity of cyclization has precedent in the influence of sodium acetate on the $\text{Pd}(\text{II})$ -promoted reactions of 2-allylphenols,¹²² and must arise because of competing coordination at palladium during the cyclization.

The specific ortho functionalization of arylamines is obviously important in quinoline synthesis (cf. the π -allyl procedure devised for the preparation of *o*-allylanilines used as indole and quinoline precursors).⁷⁶ Recently acetanilides have been subjected to orthopalladation and the ensuing complexes converted into useful precursors of 2-substituted quinoline derivatives (Scheme 143).²¹⁵

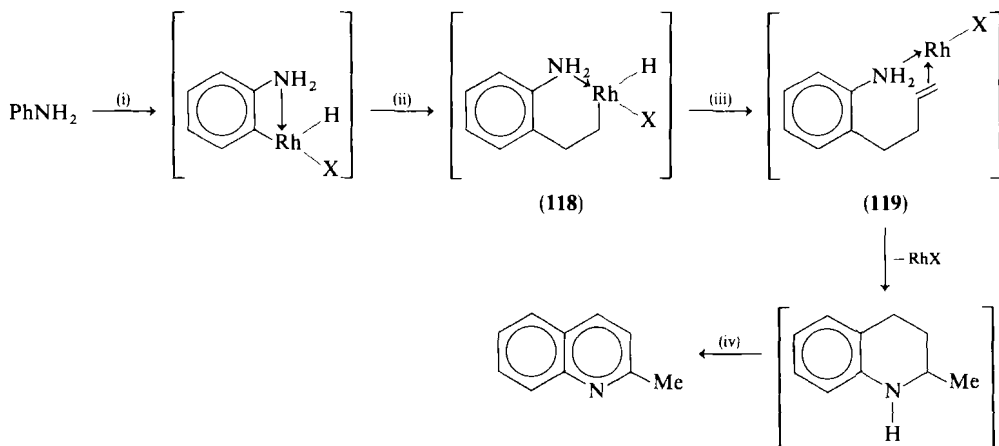
SCHEME 143. (i) $\text{CH}_2=\text{CHX}$ (X = e.g., COMe), (ii) conc. HCl.

An initial step of orthometallation probably also occurs when aniline is allowed to react with ethylene in the presence of a rhodium(I) catalyst. 2-Methylquinoline (10 turnovers relative to the metal) and *N*-ethylaniline (30 turnovers) are formed after 72 h in what are probably two independent reaction pathways (Scheme 144).²¹⁶ It is interesting to note that the intramolecular cyclization step in the proposed²¹⁶ mechanism (Scheme 144) has precedent in the palladium-promoted quinoline synthesis reported by Hegedus *et al.*⁷⁶ (see Scheme 142), but the transformation **118** \rightarrow **119** is unusual in the chemistry of organometallic insertion reactions.¹⁰⁶

The preparation of quinoline and tetrahydroquinoline derivatives from metal carbonyl-catalyzed reactions of Schiff bases with alkyl vinyl ethers in

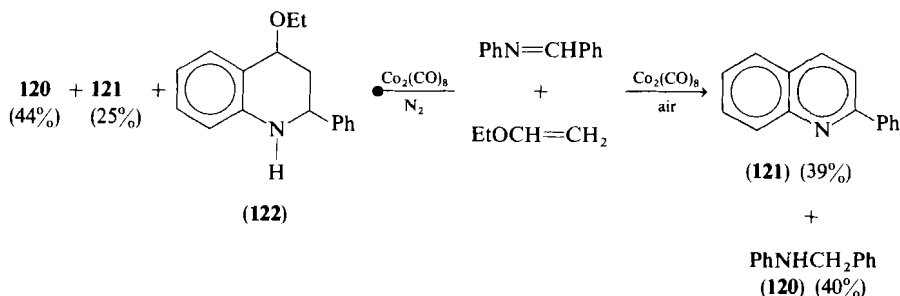
²¹⁵ H. Horino and N. Inoue, *Tetrahedron Lett.*, 2403 (1979).

²¹⁶ S. E. Diamond, A. Szalkiewicz, and F. Mares, *J. Am. Chem. Soc.* **101**, 490 (1979).



SCHEME 144. (i) RhCl_3 , Ph_3P ; (ii) C_2H_4 ; (iii) C_2H_4 ; (iv) RhX , C_2H_4 .

illustrated in Scheme 145,²¹⁷⁻²¹⁹ If the reaction is carried out under a nitrogen atmosphere, a tetrahydro derivative (**122**) is also formed, and this compound can be converted in a separate reaction with dicobalt octacarbonyl into 2-phenylquinoline. Electron-releasing groups in the *N*-aryl ring (e.g., 4-OMe) increase the yield of the quinoline product (to 78%) whereas quinoline formation is inhibited by electron-attracting groups (e.g., 4-Cl, 4- CO_2Me). It is interesting to note that when nickel carbonyl is used as a catalyst, the products are tetrahydroquinolines (cf. **122**) and the electronic substituent effect is unimportant. Cyclization reactions of this type probably



SCHEME 145

²¹⁷ T. Joh and N. Hagihara, *Tetrahedron Lett.*, 4199 (1967).

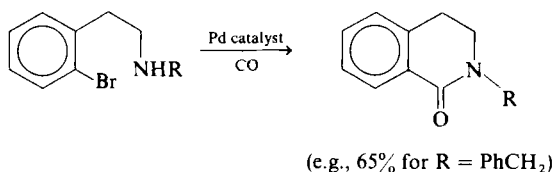
²¹⁸ T. Joh and N. Hagihara, *Nippon Kagaku Zasshi* **91**, 378 (1970) [*CA* 73, 45294 (1970)].

²¹⁹ T. Joh and N. Hagihara, *Nippon Kagaku Zasshi* **91**, 383 (1970) [*CA* 73, 45295 (1970)].

occur by a mechanism involving coordination of the imino group to a metal carbonyl species with resultant activation of the ligand to electrophilic attack by the vinyl ether; the electronic substituent effect is in accord with ensuing electrophilic attack on the *N*-aryl ring. This method offers an alternative approach to the use of boron trifluoride etherate as a catalyst for cyclizations of this type.^{220,221}

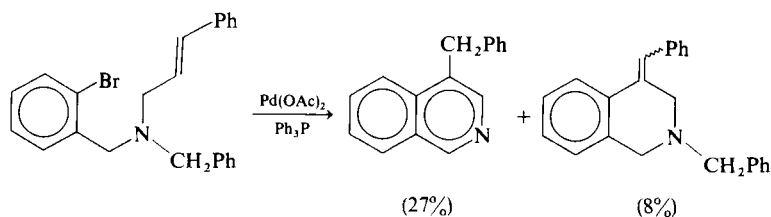
4. Isoquinolines

The mechanism of palladium-catalyzed intramolecular cyclization of *o*-bromo(aminoalkyl)benzenes has been discussed earlier (see Scheme 50 in Section IV,A,4). This approach is illustrated by the preparation of 1,2,3,4-tetrahydroisoquinolin-1-ones in Scheme 146,⁸⁶ and examples of applications in benzazepinone synthesis are given later (see Scheme 173 in Section VI,B).



SCHEME 146

Catalysis by organopalladium complexes has also been used to effect cyclization of appropriately substituted bromarylamines into indoles (cf. Scheme 44 in Section IV,A,3).⁷³ By extending the side chain by one methylene unit, the method can be applied to the synthesis of isoquinolines (Scheme 147) but the preparative scope has not been evaluated.⁷³

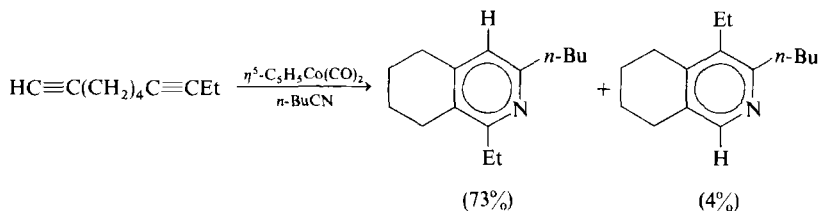


SCHEME 147

²²⁰ L. S. Povarov and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 955 (1963).

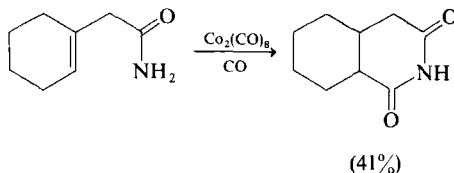
²²¹ L. S. Pavolov, V. I. Grigos, R. A. Karakhanov, and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 365 (1965).

The cobalt-catalyzed cooligomerization of diynes with nitriles allows a simple one-step synthesis²²² of condensed pyridine derivatives including difficultly accessible 5,6,7,8-tetrahydroisoquinolines²²³. The synthesis is a versatile one in that pyridines condensed with five- and seven-membered carbocyclic rings can also be achieved in moderate yield in similar fashion. Additional attractive features of this simple synthesis are the formation of condensed isoquinolines by the use of functionalized nitriles and the pronounced regioselectivity observed when dissymmetrical diacetylenes are employed (Scheme 148).²²²



SCHEME 148

A specific synthesis of 1,3-dioxohexahydroisoquinoline employing a conventional oxo hydrocarboxylation process is outlined in Scheme 149.²²⁴



SCHEME 149

B. WITH OXYGEN AS HETEROATOM

1. *Pyrans*

Pyran syntheses can be conveniently discussed on the basis of catalytic processes, and in terms of reactions that involve stoichiometric processes on preformed organometallic compounds.

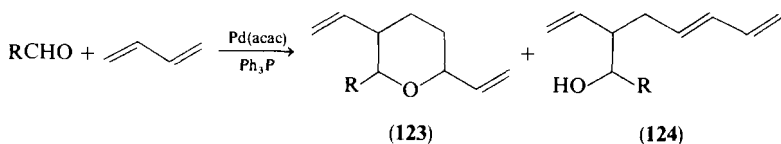
The palladium-catalyzed cooligomerization of butadiene with aldehydes provides a convenient synthesis of 2,5-divinyltetrahydropyran isomers

²²² A. Naiman and K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.* **16**, 708 (1977).

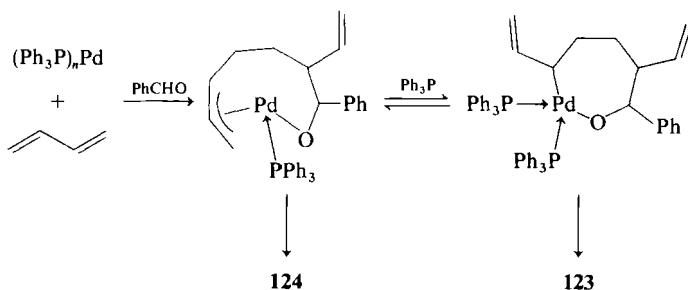
²²³ F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.* **40**, 2729 (1975).

²²⁴ J. Falbe and F. Korte, *Chem. Ber.* **95**, 2680 (1962).

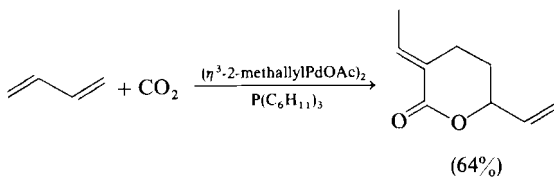
(Scheme 150).²²⁵⁻²²⁷ The pyran products predominate when the ratio of triphenylphosphine to palladium catalyst exceeds two whereas the linear oligomers are the major products when this ratio is close to unity. The suggested²²⁷ mechanism (Scheme 151) includes a step of insertion of C=O into a C—Pd σ -bond, and analogous processes probably occur during palladium-catalyzed reactions leading to the formation of pyranones (see Scheme 152)²²⁸ and piperidones (see Scheme 139 in Section V,A,2).²¹¹ It is useful to note that the 2,5-divinyltetrahydropyran derivative can be transformed catalytically by ruthenium trichloride into synthetically useful 3,4-dihydro-2H-pyran derivatives (Scheme 153).²²⁹



SCHEME 150



SCHEME 151



SCHEME 152

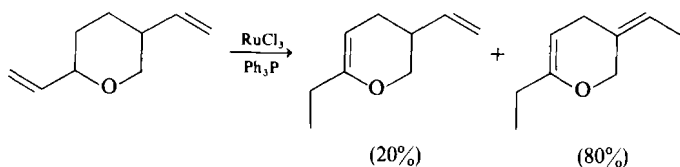
²²⁵ P. Haynes, *Tetrahedron Lett.*, 3687 (1970).

²²⁶ R. M. Manyik, W. E. Walker, K. E. Atkins, and E. S. Hammack, *Tetrahedron Lett.*, 3818 (1970).

²²⁷ K. Ohno, T. Mitsuyasu, and J. Tsuji, *Tetrahedron Lett.*, 67 (1971).

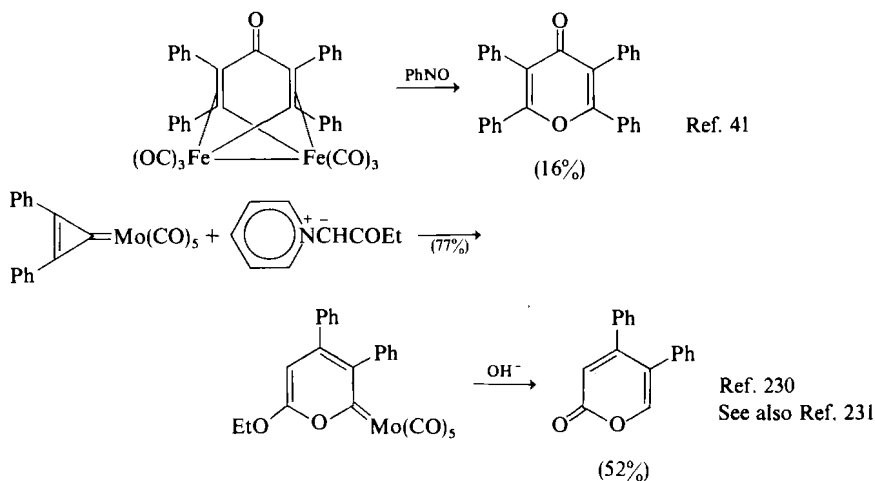
²²⁸ A. Musco, C. Perego, and V. Tartari, *Inorg. Chim. Acta* **28**, L147 (1978).

²²⁹ T. D. J. D'Silva, W. E. Walker, and R. W. Manyik, *Tetrahedron* **30**, 1015 (1974).



SCHEME 153

Stoichiometric reactions leading to the formation of pyranones and pyrans are illustrated in Scheme 154,^{41,230} but few synthetic applications can be envisaged for processes of this type.



SCHEME 154

2. Condensed Pyrans

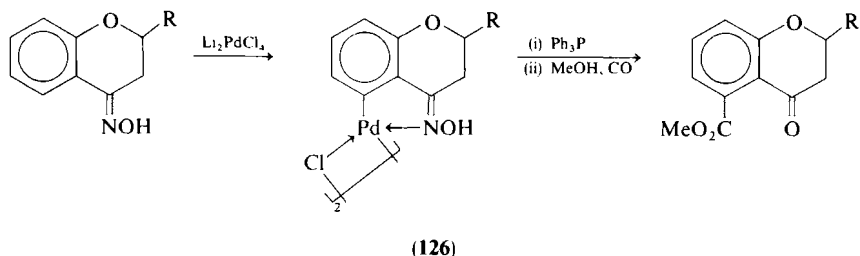
The orthometallation-carbonylation sequence illustrated in Scheme 155 affords a useful regiospecific methoxycarbonylation of the aryl ring of 4-chromanones.²³² Unfortunately an extra step is incurred in the synthesis because of the unreactivity of the dimeric complexes (**126**) toward carbonyl insertion.

The regiospecificity of intramolecular palladium-induced cyclization of *o*-allylphenols is determined by the precise nature of the catalyst. A mixture

²³⁰ T. L. Gilchrist, R. Livingston, C. W. Rees, and E. von Angerer, *J. C. S. Perkin I*, 2535 (1973); see Ref. 231 for an example of the synthesis of a completed pyran derivative.

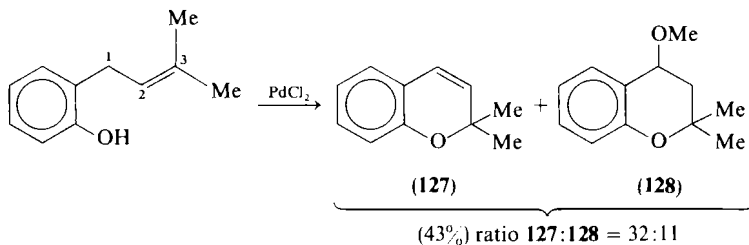
²³¹ B. L. Booth and R. G. Hargreaves, *J. Chem. Soc. A*, 308 (1970).

²³² T. Izumi, T. Katou, A. Fasahara, and K. Hanaya, *Bull. Chem. Soc. Jpn.*, **51**, 3407 (1978).



SCHEME 155

of five- (cf. Scheme 70 in Section IV,B,4) and six-membered ring compounds is formed in the PdCl_2 -mediated cyclization of 2-(3-methyl-2-butenyl)phenol (Scheme 156)¹²² By adding sodium acetate, the total product yield is in-

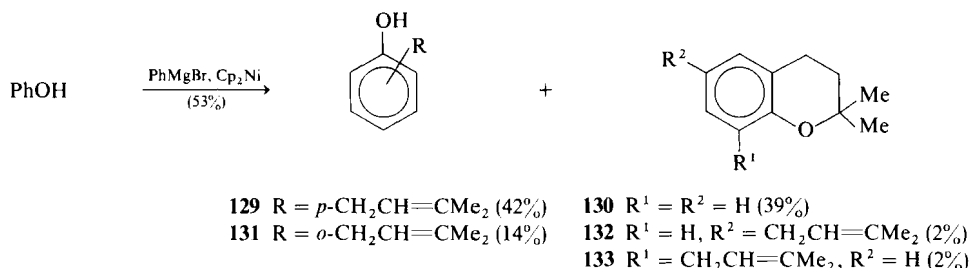


SCHEME 156

creased, and from experiments using other sodium salts it has been shown that the regioselectivity correlates with the $\text{p}K_a$ values of the appropriate carboxylic acids: the effect of an electron-withdrawing group (R in RCO_2Na) is to cause a relative increase in yield of the six-membered ring products whereas equal amounts of five- and six-membered ring compounds are formed if R is an electron-releasing group. It appears that the electron distribution at palladium in the intermediate complex causes pronounced differences in reactivity at C-2 and C-3 of the coordinated olefin ligand. A related type of intramolecular oxymetallation is probably involved in the formation of a chroman as one product in a complex mixture (129–133) formed from the reaction of phenol with isoprene catalyzed by phenylmagnesium bromide and nickelocene²³³ (Scheme 157).

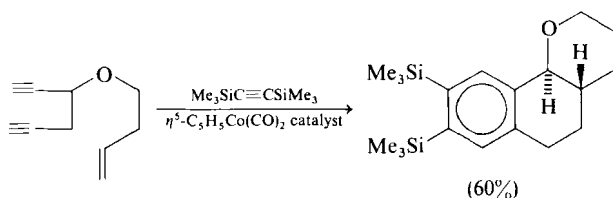
Organometallic reactions leading to condensed pyrans containing three or more rings have been achieved by cyclooligomerization processes and by intramolecular coupling. The former type of reaction is based on intramolecular trapping of *o*-xylylenes produced in cobalt-catalyzed cyclization

²³³ K. Suga, S. Watanabe, H. Kikuchi, and K. Hijikata, *J. Appl. Chem.* **20**, 175 (1970).



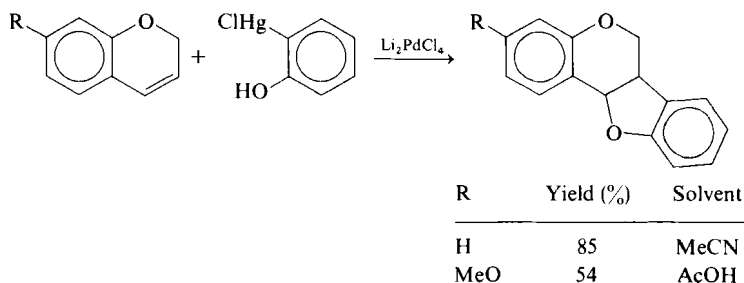
SCHEME 157

of appropriately substituted 1,5-hexadiynes (Scheme 158).²³⁴ The trimethylsilyl groups can be quantitatively removed (CF₃CO₂H-CCl₄) and the procedure is attractive compared to alternative approaches based on reactions of benzocyclobutenes. It is notable that the stereochemistry of ring fusion is almost always trans.



SCHEME 158

The novel synthesis of chromanocoumarans illustrated in Scheme 159 constitutes a modification of the Heck arylation process (cf. Eq. 14 in Section IV,B,1) in which arylation of a 2*H*-chroman is followed by intramolecular nucleophilic displacement of the palladium moiety.²³⁵



SCHEME 159

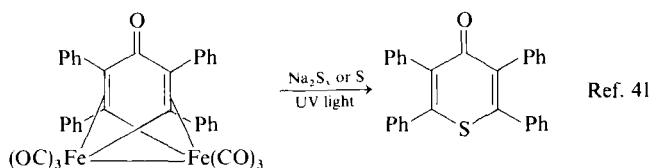
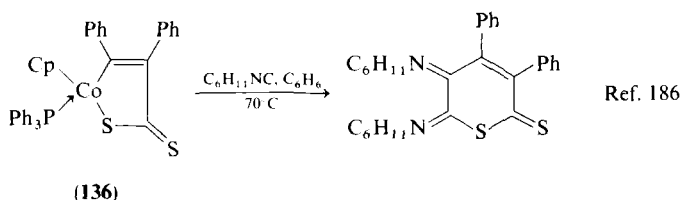
²³⁴ R. L. Funk and K. P. C. Vollhardt, *J. Am. Chem. Soc.* **98**, 6755 (1976).

²³⁵ H. Horino and N. Inoue, *J. C. S. Chem. Commun.*, 500 (1976).

C. WITH SULFUR AS HETEROATOM

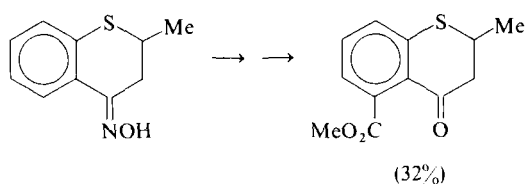
Thiapyrans and Thiachromans

Thiapyran derivatives can be prepared from preformed organoiron and -cobalt complexes as in Scheme 160; the organocobalt complex (136) can be used as an intermediate in the synthesis of 1,2-dithia cyclopent-4-en-3-thione (See Scheme 122 in Section IV,H.)



SCHEME 160

The orthometallation-carbonylation sequence described earlier (Scheme 155) has been used to effect regiospecific methoxycarbonylation of 4-thiachromanones (Scheme 161).²³²



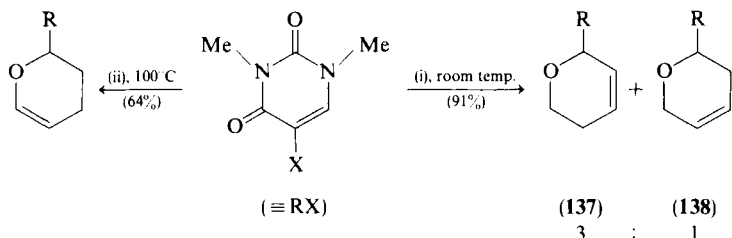
SCHEME 161

D. WITH TWO HETEROATOMS (N,N)

1. *Pyrimidines*

Pyrimidinyl palladium reagents, prepared *in situ* from mercuric or iodo derivatives, react with 3,4-dihydro-2*H*-pyran to form isomeric products containing a dihydropyranyl group attached to C-5 of the substituted uracil

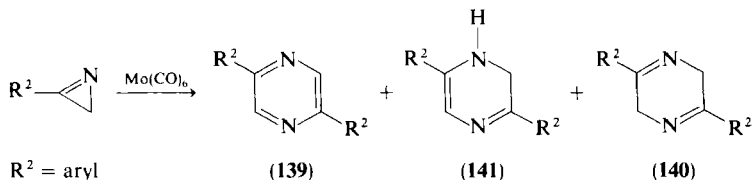
moiety (Scheme 162).²³⁶ The major isomer (**137**) is presumably formed by addition of the organopalladium species across the C=C bond of the pyran followed by elimination of a palladium hydride; the higher reaction temperature may cause the formation of a different isomer but it is surprising that neither type of process leads to formation of a conjugated isomer. Reactions of this type may find application for the synthesis of new C-nucleosides of pharmacological interest.



SCHEME 162. (i) $\text{Li}_2\text{Pd}(\text{OAc})_2\text{Cl}_2$, dihydropyran, MeCN, $\text{X} = \text{HgOAc}$; (ii) $(\text{Ph}_3\text{P})_2\text{Pd}(\text{OAc})_2$, dihydropyran, $\text{X} = \text{I}$.

2. Pyrazines

The ring cleavage of 3-aryl-2-substituted-2*H*-azirines by molybdenum hexacarbonyl has been described earlier in regard to the synthesis of pyrroles, pyrazoles and isoxazoles. In contrast to this behavior, analogous reactions of 2-unsubstituted derivatives lead to the formation of mixtures of 2,5-diarylpyrazines (**139**) and isomeric 3,6- and 1,6-dihydropyrazine derivatives (**140**, **141**) (Scheme 163).^{47,53} It is possible that the pyrazine products are formed by an intermolecular nitrene mechanism akin to the intramolecular processes described earlier (see Scheme 22 in Section IV,A,1).



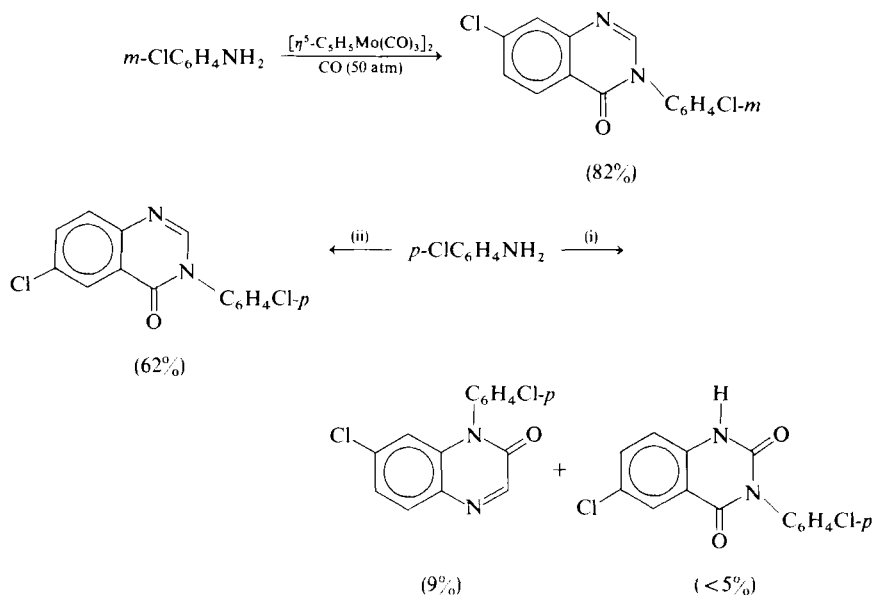
SCHEME 163

3. Quinazolines and Quinoxalines

The unusual reactivity pattern of benzylamine and carbon tetrachloride under the influence of metal carbonyl catalysts is paralleled by the behavior

²³⁶ I. Arai and G. D. Daves, *J. Org. Chem.* **43**, 4110 (1978).

of arylamines²³⁷ (cf. Scheme 104 in Section IV,D,5 and Scheme 164). Whereas aniline reacts with carbon tetrachloride in the presence of metal carbonyl catalysts to give an amidine derivative, *m*-chloroaniline is converted into a quinazoline derivative under similar conditions; *p*-chloroaniline behaves in similar fashion at relatively low carbon monoxide pressure, but at higher pressure a mixture of a quinazolidinedione and a quinoxalinone is formed, albeit in low yield. Quinazolidinediones are obtained as the sole products from *m*- and *p*-toluidines and from 3,5-xylidine but yields are poor. The suggestion²³⁷ that the products shown in Scheme 164 arise by free radical mechanisms has not yet been substantiated. It would be of interest to ascertain whether this type of cyclization could be applied to aminoheterenes with a view to the synthesis of more complex condensed pyrimidines and pyrazines.

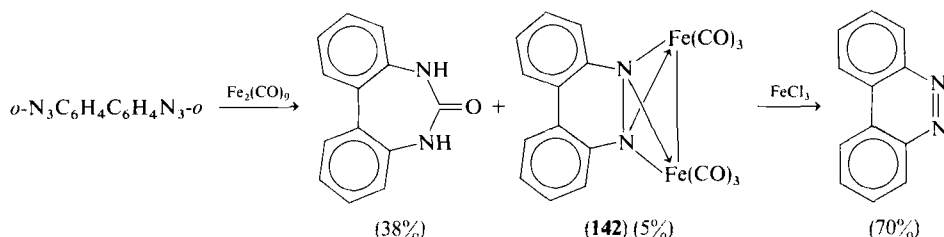


SCHEME 164. (i) Mo(CO)_6 , CCl_4 , CO (150 atm); (ii) Mo(CO)_6 , CCl_4 , CO (100 atm).

4. Condensed Cinnolines

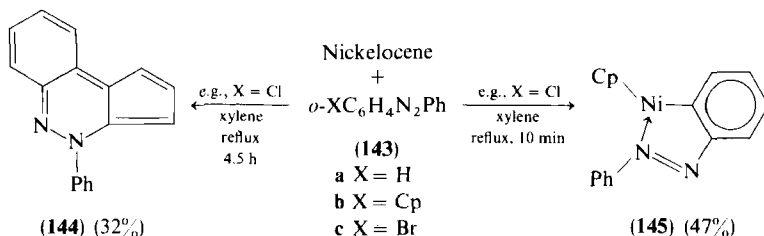
2,2'-Diazidobiphenyl is transformed by diiron nonacarbonyl into a cyclic urea together with a small amount of the bridged dinuclear complex **142**; the latter is a minor product but it can be converted oxidatively into benzocinnoline (Scheme 165).¹⁹¹

²³⁷ Y. Mori and J. Tsuji, *Tetrahedron* **27**, 3811 (1971).



SCHEME 165

A novel annellation leading to 4-phenyl-4*H*-cyclopenta[*c*]cinnoline (**144**) has been observed when nickelocene is allowed to react with excess of an azoarene (**143a–c**) (Scheme 166).^{2,38} The reactions are facilitated by the presence of an ortho halogen substituent in the azoarene derivative (**143b,c**), and depending on reaction time, the product may be an orthometallated complex (**145**) or the heterocycle **144**; the latter can also be obtained by oxidation of the complex with perbenzoic acid. It is apparent from subsequent experiments^{2,38} that the ArN–NAr skeleton of the product **144** originates from the complex, and not the excess azoarene, hence the latter acts as a hydrogen acceptor. This type of cyclopentadienyl insertion via orthometallation is unique in heterocyclic synthesis, and an evaluation of the scope of such processes is desirable.



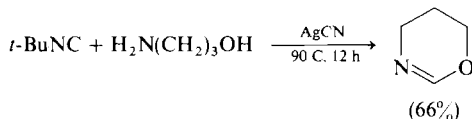
SCHEME 166

E. WITH TWO HETEROATOMS (N,O)

Oxazines and Benzoxazines

The silver cyanide-catalyzed reaction of difunctional nucleophiles with tert-butyl isocyanide has been described in earlier sections on azoles (see Scheme 105 in Section IV,D,6). An example of the use of this simple approach

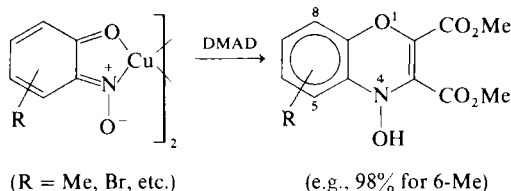
^{2,38} Yu A. Ustynyuk and I. V. Barinov, *J. Organomet. Chem.* **23**, 551 (1970).



SCHEME 167

for the synthesis of 5,6-dihydro-4*H*-1,3-oxazine is illustrated in Scheme 167.¹⁶⁹

Readily available copper(II) complexes derived from *o*-nitrosophenols react with dimethyl acetylenedicarboxylate to give the 1,4-benzoxazine products that would be expected from formal [4 + 2] cycloaddition across the diheterodiene system (Scheme 168).²³⁹ No such reaction is observed in blank experiments with uncomplexed tautomeric nitrosophenols hence the copper may cause sufficient electronic perturbation within the heterodiene complex to allow reaction to occur.

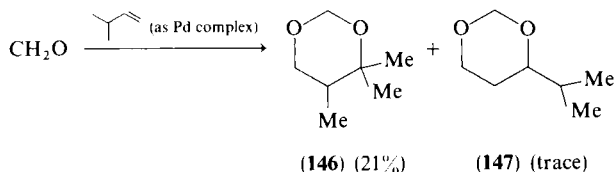


SCHEME 168

F. WITH TWO HETEROATOMS (O,O)

Dioxanes

4,4,5-Trimethyl-1,3-dioxane (**146**) is the major product formed when the palladium complex of 3-methyl-1-butene is treated with formaldehyde. The dioxane products (**146**, **147**) can also be obtained directly in improved yield from the olefin using the catalytic system PdCl₂-CuCl₂ (Scheme 169).²⁴⁰



SCHEME 169

²³⁹ A. McKillop and T. S. B. Sayer, *J. Org. Chem.* **41**, 1079 (1976).

²⁴⁰ S. Sakai, Y. Kawashima, Y. Takahashi, and Y. Ishii, *Chem. Commun.*, 1073 (1967). *Kogyo Kagaku Zasshi* **72**, 1715 (1969) [*CA* **72**, 21646 (1970)].

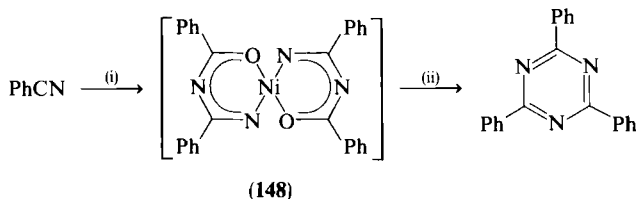
The limitation on this simple dioxan synthesis is that unbranched olefins are unreactive. Nevertheless, the method offers advantages over the alternative acid-catalyzed (Prins) reaction in regard to both product yield and selectivity.

G. WITH THREE HETEROATOMS

s-Triazines

By analogy with the cyclotrimerization of acetylenes into arenes, and with the cocyclooligomerization of nitriles and acetylenes into pyridines (see Scheme 131 in Section V,A,1), the cyclization of benzonitrile into 2,4,6-triphenyl-*s*-triazine can be achieved by means of $\text{Fe}(\text{CO})_5$ or $\text{Fe}_2(\text{CO})_9$.²⁴¹

Benzonitrile is also trimerized to the *s*-triazine derivative by Raney nickel²⁴² in a reaction which may proceed via the coordination compound (148)²⁴³; in a separate experiment this complex reacts with benzonitrile in the presence of benzamide to give the trimer (Scheme 171)²⁴²



SCHEME 171. (i) Raney Ni, reflux; (ii) recrystallize from AcOH or PhCN, reflux.

VI. Seven-Membered Ring Compounds

A. WITH SILICON AS HETEROATOM

Condensed Silepins

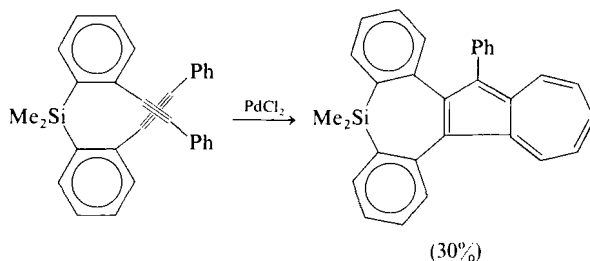
The diyne reaction has been used extensively by Müller *et al.* in heterocyclic synthesis (see for example Scheme 86 in Section IV,C,2); a process using a diyne substrate and leading to the formation of an azuleno[1,2-*d*]-dibenzo[*b, f*]silepin is shown in Scheme 172.^{243a}

²⁴¹ S. F. A. Kettle and L. E. Orgel, *Proc. Chem. Soc., London*, 307 (1959).

²⁴² W. Z. Heldt, *J. Organomet. Chem.* **6**, 292 (1966).

²⁴³ G. Oehme and H. Pracejus, *Z. Chem.* **9**, 140 (1969).

^{243a} E. Müller and G. Zountsas, *Chem. Ztg* **97**, 447 (1973).

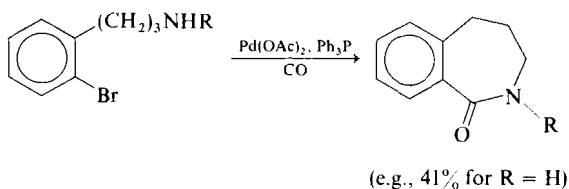


SCHEME 172

B. WITH NITROGEN AS HETEROATOM

Benzazepins

The mechanism of palladium-catalyzed intramolecular cyclization of *o*-bromo(aminoalkyl)benzenes has been discussed earlier (see Scheme 50 in Section IV,A,4). An example illustrating the use of this approach for the synthesis of 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-ones is given in Scheme 173⁸⁶ and examples indicating the synthesis of isoquinoline derivatives are given earlier (see Scheme 146 in Section V,A,4).



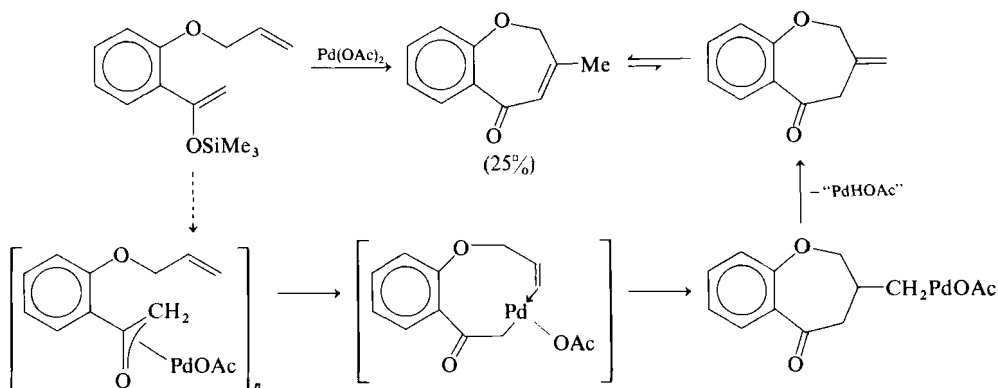
SCHEME 173

C. WITH OXYGEN AS HETEROATOM

Condensed Oxepins

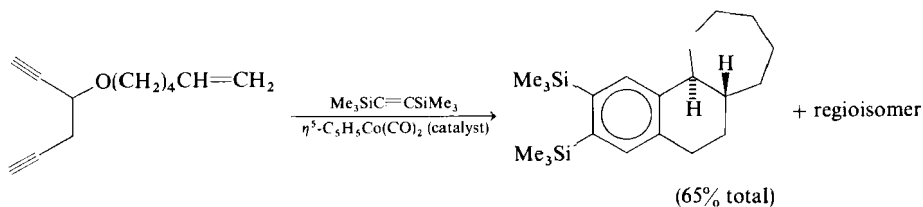
Silyl enol ethers of alkenyl methyl ketones can be efficiently cyclized to cyclopentenones and cyclohexenones by treating them with stoichiometric amounts of palladium acetate²⁴⁴; an example indicating the elaboration of this approach to the synthesis of a reduced benzoxepinone derivative, and the suggested²⁴⁴ mechanism of the reaction, are depicted in Scheme 174.

²⁴⁴ Y. Ito, H. Aoyama, T. Hirao, A. Mochizuki, and T. Saegusa, *J. Am. Chem. Soc.* **101**, 494 (1979).



SCHEME 174

An example illustrating the synthesis of condensed oxepins by the cobalt-catalyzed reaction of bistrimethylsilylacetylene with a hexa-1,5-diyne derivative is shown in Scheme 175.²³⁴ This type of process has been discussed earlier in the context of pyran synthesis (see Scheme 158 in Section V,B,2).



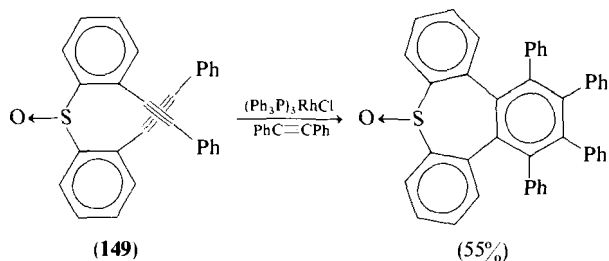
SCHEME 175

D. WITH SULFUR AS HETEROATOM

Condensed Thiepins

A variety of heterocyclic compounds has been synthesized via condensed rhodacyclopentadienes (the "diyne reaction") (see for example Scheme 86 in Section IV,C,2). An example of the application of this type of process leading to the formation of a tribenzothiepin is outlined in Scheme 176.²⁴⁵ The bisacetylene derivative **149** can also be converted into a dibenzo[*b,f*]azuleno[1,2-*d*]thiepin derivative by means of (PhCN)₂PdCl₂ (cf. Scheme 172 in Section VI,A).

²⁴⁵ E. Müller and G. Zountsas, *Chem. Ztg.* **98**, 41 (1974).

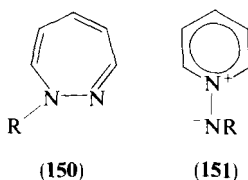


SCHEME 176

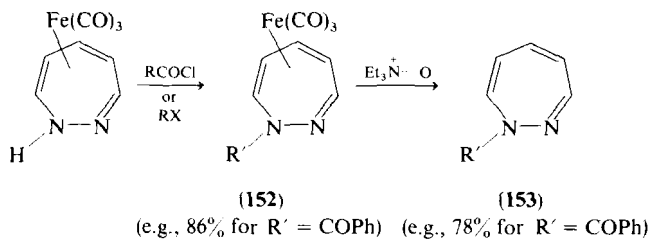
E. WITH TWO HETEROATOMS (N,N)

Diazepines and Benzodiazepines

1*H*-1,2-Diazepines (150) can be prepared by ultraviolet photolysis of *N*-iminopyridinium ylids (151) but N—N bond homolysis in the ylid substrates presents a problem in regard to the synthesis of N-1 substituted



derivatives. This situation can be alleviated by effecting N-1 acylation and alkylation via readily accessible²⁴⁶ tricarbonyl (4-7- η -1*H*-1,2-diazepine) iron(0) and deligation of ensuing tricarbonyliron adducts (Scheme 178).²⁴⁷



SCHEME 178

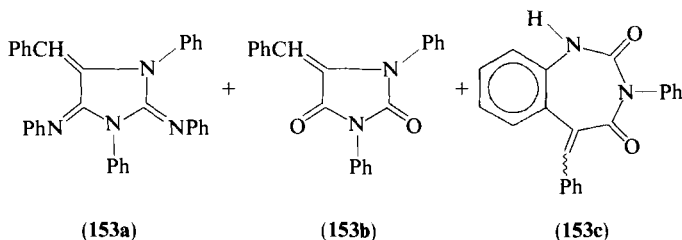
²⁴⁶ A. J. Carty, R. F. Hobson, H. A. Patel, and V. Snieckus, *J. Am. Chem. Soc.* **95**, 6835 (1973);

A. J. Carty, C. R. Jablonski, and V. Snieckus, *Inorg. Chem.* **15**, 601 (1976).

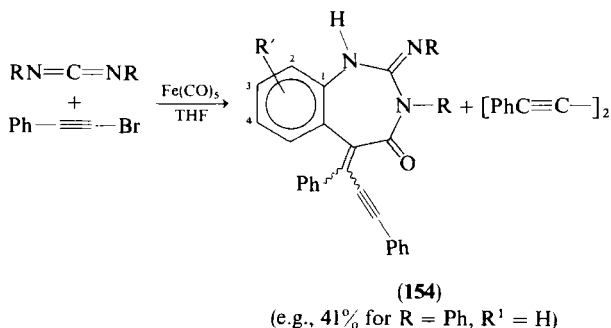
²⁴⁷ D. J. Harris and V. Snieckus, *J. C. S. Chem. Commun.*, 844 (1976).

Decomplexation of **152** ($R' = \text{CH}_2\text{Ph}$) affords the labile **153** ($R' = \text{CH}_2\text{Ph}$) which is the first example of a simple *N*-alkyl-1*H*-1,2-diazepine.

A benzodiazepine-2-4-dione derivative (**153c**) is formed as a minor product (12%) in a mixture containing imidazolidines (**153a, b**) from the iron penta-



carbonyl-induced cooligomerization of diphenylcarbodiimide with phenylacetylene.¹⁶⁶ Better yields of benzodiazepine products (**154**) are achieved using phenylbromoacetylene¹⁶⁸ in reactions which presumably have mechanistic analogy in related processes leading to the formation of imidazolidines (Scheme 180, and cf. Schemes 100 and 101 in Section IV,D,5).

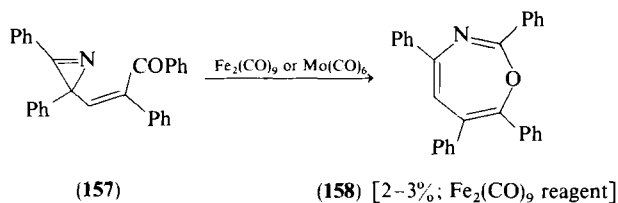


SCHEME 180

F. WITH TWO HETEROATOMS (N,O)

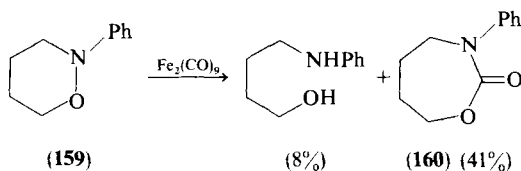
Oxazepines

A 1,3-oxazepine derivative (**158**) has been isolated in low (2–3%) or unspecified yield by treatment of the *Z*-ketovinylazirine **157** with diiron nonacarbonyl⁵⁰ or molybdenum hexacarbonyl,⁵¹ respectively (Scheme 182); the major products of these reactions are pyrrole derivatives (see Scheme 23 in Section IV,A,1). There is no preparative value in this type of oxazepine synthesis (Scheme 182) since the transformation can be affected efficiently in a thermal reaction at 100°C.⁵²



SCHEME 182

Formation of the reduced 1,3-oxazepine derivative **160** from the reaction of diiron nonacarbonyl with the tetrahydrooxazine derivative (**159**) involves a novel formal insertion of carbon monoxide into an N—O bond (Scheme 183).²⁴⁸ The synthetic applicability of this unusual reaction has not been evaluated.

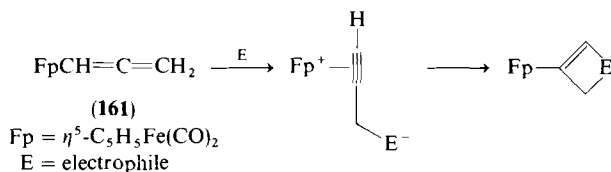


SCHEME 183

G. WITH THREE HETEROATOMS

Oxathiazepines

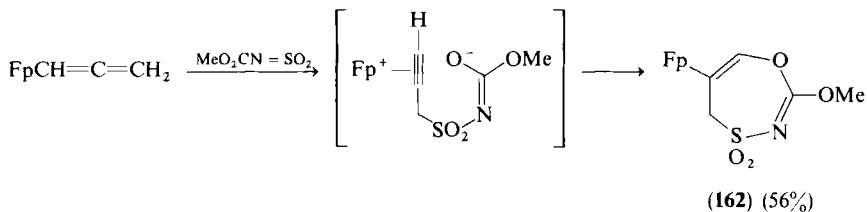
The mechanism and synthetic utility of reactions of monohaptoallyl- and monohaptopropargyliron complexes with electrophiles have been discussed earlier (see Schemes 30–33 in Section IV,A,2). By analogy with these processes, monohaptoallenyliron complexes (**161**) react with electrophiles (E) in the manner depicted in Scheme 184; an example of this type of reaction



SCHEME 184

²⁴⁸ Y. Becker, A. Eisenstadt, and Y. Shvo, *Tetrahedron* **30**, 839 (1974).

leading to the formation of an oxathiazepin derivative is illustrated in Scheme 185.¹⁷⁹ No attempt has been made to remove the Fp moiety from the heterocycle (**162**) but successful use of the reagent PhSH-NaOMe for C—Fe cleavage in analogous pyrrolidones has been noted earlier⁶⁰ (see Section IV,A,2).

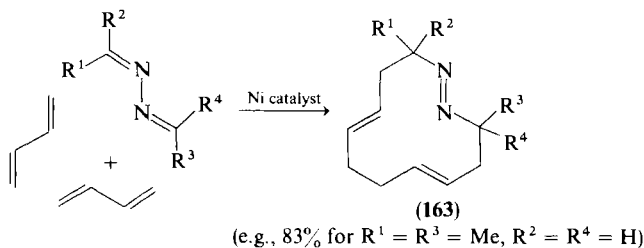


SCHEME 185

VII. Macrocycles

1,2-DIAZA-1,5,9-CYCLODECATRIENES

A number of compounds with this ring system (**163**), including dispiro derivatives, are formed by the catalytic cooligomerization of ketazines or aldazines with butadiene (Scheme 186)²⁴⁹; reactions of this type are analogous to the catalytic cyclotrimerization of butadiene to cyclodecatriene.²⁵⁰



SCHEME 186

²⁴⁹ P. Heimbach, B. Hugelin, H. Peter, A. Roloff, and E. Troxler, *Angew. Chem., Int. Ed. Engl.* **15**, 49 (1976).

²⁵⁰ R. Baker, *Chem. Rev.* **73**, 487 (1973).

Cumulative Index of Titles

A

- Acetylenecarboxylic acids and esters, reactions with *N*-heterocyclic compounds, **1**, 125
- Acetylenecarboxylic esters, reactions with nitrogen-containing heterocycles, **23**, 263
- Acetylenic esters, synthesis of heterocycles through nucleophilic additions to, **19**, 297
- Acid-catalyzed polymerization of pyrroles and indoles, **2**, 287
- t*-Amino effect, **14**, 211
- Aminochromes, **5**, 205
- Anils, olefin synthesis with, **23**, 171
- Annulenes, N-bridged, cyclazines and, **22**, 321
- Anthracen-1,4-imines, **16**, 87
- Anthranils, **8**, 277; **29**, 1
- Applications of NMR spectroscopy to indole and its derivatives, **15**, 277
- Applications of the Hammett equation to heterocyclic compounds, **3**, 209; **20**, 1
- Aromatic azapentalenes, **22**, 183
- Aromatic quinolizines, **5**, 291
- Aromaticity of heterocycles, **17**, 255
- Aza analogs of pyrimidine and purine bases, **1**, 189
- 7-Azabicyclo[2.2.1]hepta-2,5-dienes, **16**, 87
- 1-Azabicyclo[3.1.0]hexanes and analogs with further heteroatom substitution, **27**, 1
- Azapentalenes, aromatic, chemistry of, **22**, 183
- Azines, reactivity with nucleophiles, **4**, 145
- Azines, theoretical studies of, physicochemical properties of reactivity of, **5**, 69
- Azinoazines, reactivity with nucleophiles, **4**, 145
- 1-Azirines, synthesis and reactions of, **13**, 45
- Azodicarbonyl compounds in heterocyclic synthesis, **30**, 1

B

- Base-catalyzed hydrogen exchange, **16**, 1
- 1-, 2-, and 3-Benzazepines, **17**, 45

- Benzisothiazoles, **14**, 43
- Benzisoxazoles, **8**, 277
- Benzoazines, reactivity with nucleophiles, **4**, 145
- Benzo[*c*]cinnolines, **24**, 151
- 1,5-Benzodiazepines, **17**, 27
- Benzo[*b*]furan and derivatives, recent advances in chemistry of, Part I, occurrence and synthesis, **18**, 337
- Benzo[*c*]furans, **26**, 135
- Benzofuroxans, **10**, 1; **29**, 251
- 2*H*-Benzopyrans (chrom-3-enes), **18**, 159
- 1,2- and 2,1-Benzothiazines and related compounds, **28**, 73
- Benzo[*b*]thiophene chemistry, recent advances in, **11**, 177; **29**, 171
- Benzo[*c*]thiophenes, **14**, 331
- 1,2,3-(Benzo)triazines, **19**, 215
- Benzyne, reactions with heterocyclic compounds, **28**, 183
- Biological pyrimidines, tautomerism and electronic structure of, **18**, 199

C

- Carbenes
and nitrenes, intramolecular reactions, **28**, 231
reactions with heterocyclic compounds, **3**, 57
- Carbolines, **3**, 79
- Cationic polar cycloaddition, **16**, 289 (**19**, xi)
- Chemistry
of aromatic azapentalenes, **22**, 183
of benzo[*b*]furan, Part I, occurrence and synthesis, **18**, 337
of benzo[*b*]thiophenes, **11**, 177; **29**, 171
of chrom-3-enes, **18**, 159
of diazepines, **8**, 21
of dibenzothiophenes, **16**, 181
of 1,2-dioxetanes, **21**, 437
of furans, **7**, 377
of isatin, **18**, 1
of isoxazolidines, **21**, 207
of lactim ethers, **12**, 185
of mononuclear isothiazoles, **14**, 1
of 4-oxy- and 4-keto-1,2,3,4-tetrahydroisoquinolines, **15**, 99
of phenanthridines, **13**, 315

Chemistry (Cont.)

- of phenothiazines, **9**, 321
- of 1-pyridines, **15**, 197
- of tetrazoles, **21**, 323
- of 1,3,4-thiadiazoles, **9**, 165
- of thienothiophenes, **19**, 123
- of thiophenes, **1**, 1
- Chrom-3-ene chemistry, advances in, **18**, 159
- Claisen rearrangements, in nitrogen heterocyclic systems, **8**, 143
- Complex metal hydrides, reduction of nitrogen heterocycles with, **6**, 45
- Covalent hydration
 - in heteroaromatic compounds, **4**, 1, 43
 - in nitrogen heterocycles, **20**, 117
- Current views on some physicochemical aspects of purines, **24**, 215
- Cyclazines, and related N-bridged annulenes, **22**, 321
- Cyclic enamines and imines, **6**, 147
- Cyclic hydroxamic acids, **10**, 199
- Cyclic peroxides, **8**, 165
- Cycloaddition, cationic polar, **16**, 289 (**19**, xi)
- (2 + 2)-Cycloaddition and (2 + 2)-cyclo-reversion reactions of heterocyclic compounds, **21**, 253

D

- Developments in the chemistry
 - of furans (1952–1963), **7**, 377
 - of Reissert compounds (1968–1978), **24**, 187
- 2,4-Dialkoxypyrimidines, Hilbert–Johnson reaction of, **8**, 115
- Diazepines, chemistry of, **8**, 21
- 1,4-Diazepines, 2,3-dihydro-, **17**, 1
- Diazirines, diaziridines, **2**, 83; **24**, 63
- Diazo compounds, heterocyclic, **8**, 1
- Diazomethane, reactions with heterocyclic compounds, **2**, 245
- Dibenzothiophenes, chemistry of, **16**, 181
- 2,3-Dihydro-1,4-diazepines, **17**, 1
- 1,2-Dihydroisoquinolines, **14**, 279
- 1,2-Dioxetanes, chemistry of, **21**, 437
- Diquinolylmethane and its analogs, **7**, 153
- 1,2- and 1,3-Dithiolium ions, **7**, 39; **27**, 151

E

- Electrolysis of N-heterocyclic compounds, **12**, 213
- Electronic aspects of purine tautomerism, **13**, 77
- Electronic structure of biological pyrimidines, tautomerism and **18**, 199
- Electronic structure of heterocyclic sulfur compounds, **5**, 1
- Electrophilic substitutions of five-membered rings, **13**, 235
- π -Excessive heteroannulenes, medium-large and large, **23**, 55

F

- Ferrocenes, heterocyclic, **13**, 1
- Five-membered rings, electrophilic substitutions of, **13**, 235
- Free radical substitutions of heteroaromatic compounds, **2**, 131
- Furans
 - development of the chemistry of (1952–1963), **7**, 377
 - recent advances in chemistry, Part I, **30**, 168
- Furoxans, **29**, 251

G

- Grignard reagents, indole, **10**, 43

H

- Halogenation of heterocyclic compounds, **7**, 1
- Hammett equation, applications to heterocyclic compounds, **3**, 209; **20**, 1
- Hetarynes, **4**, 121
- Heteroadamantane, **30**, 80
- Heteroannulenes, medium-large and large π -excessive, **23**, 55
- Heteroaromatic compounds
 - N-aminoazonium salts, **29**, 71
 - free-radical substitutions of, **2**, 131
 - homolytic substitution of, **16**, 123
 - nitrogen, covalent hydration in, **4**, 1, 43

- prototropic tautomerism of, 1, 311, 339; 2, 1, 27; Suppl. 1
quaternization of, 22, 71
Heteroaromatic *N*-imines, 17, 213; 29, 71
Heteroaromatic nitro compounds, ring synthesis of, 25, 113
Heteroaromatic radicals, Part I, general properties; radicals with Group V ring heteroatoms, 25, 205; Part II, radicals with Group VI and Groups V and VI ring heteroatoms, 27, 31
Heteroaromatic substitution, nucleophilic, 3, 285
Heterocycles
 aromaticity of, 17, 255
 nomenclature of, 20, 175
 photochemistry of, 11, 1
 by ring closure of ortho-substituted *t*-anilines, 14, 211
 synthesis of, through nucleophilic additions to acetylenic esters, 19, 279
 thioureas in synthesis of, 18, 99
Heterocyclic betaine derivatives of alternant hydrocarbons, 26, 1
Heterocyclic chemistry, literature of, 7, 225; 25, 303
Heterocyclic compounds
 application of Hammett equation to, 3, 209; 20, 1
 (2 + 2)-cycloaddition and (2 + 2)-cycloreversion reactions of, 21, 253
 halogenation of, 7, 1
 isotopic hydrogen labeling of, 15, 137
 mass spectrometry of, 7, 301
 quaternization of, 3, 1; 22, 71
 reactions of, with carbenes, 3, 57
 reactions of diazomethane with, 2, 245
N-Heterocyclic compounds
 electrolysis of, 12, 213
 reaction of acetylenecarboxylic acids and esters with, 1, 125; 23, 263
Heterocyclic diazo compounds, 8, 1
Heterocyclic ferrocenes, 13, 1
Heterocyclic oligomers, 15, 1
Heterocyclic pseudobases, 1, 167; 25, 1
Heterocyclic sulphur compounds, electronic structure of, 5, 1
Heterocyclic synthesis, from nitrilium salts under acidic conditions, 6, 95
Hilbert-Johnson reaction of 2,4-dialkoxy-pyrimidines, 8, 115
Homolytic substitution of heteroaromatic compounds, 16, 123
Hydrogen exchange
 base-catalyzed, 16, 1
 one-step (labeling) methods, 15, 137
Hydroxamic acids, cyclic, 10, 199
- I**
- Imidazole chemistry, advances in, 12, 103; 27, 241
Indole Grignard reagents, 10, 43
Indole(s)
 acid-catalyzed polymerization, 2, 287
 and derivatives, application of NMR spectroscopy to, 15, 277
Indolizine chemistry, advances in, 23, 103
Indolones, isatogens and, 22, 123
Indoxazenes, 8, 277; 29, 1
Isatin, chemistry of, 18, 1
Isatogens and indolones, 22, 123
Isatoic anhydrides, uses in heterocyclic synthesis, 28, 127
Isoindoles, 10, 113; 29, 341
Isoquinolines
 1,2-dihydro-, 14, 279
 4-oxy- and 4-keto-1,2,3,4-tetrahydro-, 15, 99
Isothiazoles, 14, 107
 recent advances in the chemistry of monocyclic, 14, 1
Isotopic hydrogen labeling of heterocyclic compounds, one-step methods, 15, 137
Isoxazole chemistry, recent developments in, 2, 365; since 1963, 25, 147
Isoxazolidines, chemistry of, 21, 207
- J**
- Lactim ethers, chemistry of, 12, 185
Literature of heterocyclic chemistry, 7, 225; 25, 303
- M**
- Mass spectrometry of heterocyclic compounds, 7, 301
Medium-large and large π -excessive heteroannulenes, 23, 55

Meso-ionic compounds, **19**, 1
 Metal catalysts, action on pyridines, **2**, 179
 Meso-ionic compounds, **19**, 1
 Metal catalysts, action on pyridines, **2**, 179
 Monoazaindoles, **9**, 27
 Monocyclic pyrroles, oxidation, of, **15**, 67
 Monocyclic sulfur-containing pyrones, **8**, 219
 Mononuclear heterocyclic rearrangements, **29**, 141
 Mononuclear isothiazoles, recent advances in chemistry of, **14**, 1

N

Naphthalen-1,4,imines, **16**, 87
 Naphthyridines, **11**, 124
 Nitriles and nitrilium salts, heterocyclic syntheses involving, **6**, 95
 Nitrogen-bridged six-membered ring systems, **16**, 87
 Nitrogen heterocycles
 covalent hydration in, **20**, 117
 reactions of acetylenecarboxylic esters with, **23**, 263
 reduction of, with complex metal hydrides, **6**, 45
 Nitrogen heterocyclic systems, Claisen rearrangements in, **8**, 143
 Nomenclature of heterocycles, **20**, 175
 Nuclear magnetic resonance spectroscopy, application to indoles, **15**, 277
 Nucleophiles, reactivity of azine derivatives with, **4**, 145
 Nucleophilic additions to acetylenic esters, synthesis of heterocycles through, **19**, 299
 Nucleophilic heteroaromatic substitution, **3**, 285

O

Olefin synthesis with anils, **23**, 171
 Oligomers, heterocyclic, **15**, 1
 1,2,4-Oxadiazoles, **20**, 65
 1,3,4-Oxadiazole chemistry, recent advances in, **7**, 183
 1,3-Oxazine derivatives, **2**, 311; **23**, 1
 Oxaziridines, **2**, 83; **24**, 63
 Oxazole chemistry, advances in, **17**, 99

Oxazolone chemistry
 new developments in, **21**, 175
 recent advances in, **4**, 75
 Oxidation of monocyclic pyrroles, **15**, 67
 3-Oxo-2,3-dihydrobenz[d]isothiazole-1,1-dioxide (saccharin) and derivatives, **15**, 233
 4-Oxy- and 4-keto-1,2,3,4-tetrahydro-isoquinolines, chemistry of, **15**, 99

P

Pentazoles, **3**, 373
 Peroxides, cyclic, **8**, 165 (*see also* 1,2-Dioxetanes)
 Phenanthridine chemistry, recent developments in, **13**, 315
 Phenanthrolines, **22**, 1
 Phenothiazines, chemistry of, **9**, 321
 Phenoxazines, **8**, 83
 Photochemistry
 of heterocycles, **11**, 1
 of nitrogen-containing heterocycles, **30**, 239
 Physicochemical aspects of purines, **6**, 1; **24**, 215
 Physicochemical properties
 of azines, **5**, 69
 of pyrroles, **11**, 383
 3-Piperidineines, **12**, 43
 Polyfluoroheteroaromatic compounds, **28**, 1
 Polymerization of pyrroles and indoles, acid-catalyzed, **2**, 287
 Prototropic tautomerism of heteroaromatic compounds, **1**, 311, 339; **2**, 1, 27; Suppl. 1
 Pseudobases, heterocyclic, **1**, 167; **25**, 1
 Purine bases, aza analogs of, **1**, 189
 Purines
 physicochemical aspects of, **6**, 1; **24**, 215
 tautomerism, electronic aspects of, **13**, 77
 Pyrazine chemistry, recent advances in, **14**, 99
 Pyrazole chemistry, progress in, **6**, 347
 Pyridazines, **9**, 211; **24**, 363
 Pyridine(s)
 action of metal catalysts on, **2**, 179
 effect of substituents on substitution in, **6**, 229
 1,2,3,6-tetrahydro-, **12**, 43
 Pyridoindoles (the carbolines), **3**, 79
 Pyridopyrimidines, **10**, 149

- Pyrimidine bases, aza analogs of, **1**, 189
Pyrimidines
 2,4-dialkoxy-, Hilbert-Johnson reaction of, **8**, 115
 tautomerism and electronic structure of biological, **18**, 199
1-Pyridines, chemistry of, **15**, 197
Pyrones, monocyclic sulfur-containing, **8**, 219
Pyrroles
 acid-catalyzed polymerization of, **2**, 287
 oxidation of monocyclic, **15**, 67
 physicochemical properties of, **11**, 383
Pyrrolizidine chemistry, **5**, 315; **24**, 247
Pyrrolidiazines, with a bridgehead nitrogen, **21**, 1
Pyrrolopyridines, **9**, 27
Pyrylum salts, syntheses, **10**, 241
Selenophenes, **30**, 127
Six-membered ring systems, nitrogen bridged, **16**, 87
Substitution(s)
 electrophilic, of five-membered rings, **13**, 235
 homolytic, of heteroaromatic compounds, **16**, 123
 nucleophilic heteroaromatic, **3**, 285
 in pyridines, effect of substituents, **6**, 229
Sulfur compounds, electronic structure of heterocyclic, **5**, 1
Sulfur transfer reagents in heterocyclic synthesis, **30**, 48
Synthesis and reactions of 1-azirines, **13**, 45
Synthesis of heterocycles through nucleophilic additions to acetylenic esters, **19**, 279

Q

- Quaternization
 of heteroaromatic compounds, **22**, 71
 of heterocyclic compounds, **3**, 1
Quinazolines, **1**, 253; **24**, 1
Quinolizines, aromatic, **5**, 291
Quinoxaline chemistry
 developments 1963-1975, **22**, 367
 recent advances in, **2**, 203
Quinuclidine chemistry, **11**, 473

R

- Recent advances in furan chemistry, Part I, **30**, 168
Reduction of nitrogen heterocycles with complex metal hydrides, **6**, 45
Reissert compounds, **9**, 1; **24**, 187
Ring closure of ortho-substituted *t*-anilines, for heterocycles, **14**, 211
Ring synthesis of heteroaromatic nitro compounds, **25**, 113

S

- Saccharin and derivatives, **15**, 233
Selenazole chemistry, present state of, **2**, 343
Selenium-nitrogen heterocycles, **24**, 109
Selenophene chemistry, advances in, **12**, 1

T

- Tautomerism
 electronic aspects of purine, **13**, 77
 and electronic structure of biological pyrimidines, **18**, 199
 prototropic, of heteroaromatic compounds, **1**, 311, 339; **2**, 1, 27; Suppl. 1
Tellurophene and related compounds, **21**, 119
1,2,3,4-Tetrahydroisoquinolines, 4-oxy- and 4-keto-, **15**, 99
1,2,3,6-Tetrahydropyridines, **12**, 43
Tetrazole chemistry, recent advances in, **21**, 323
Theoretical studies of physicochemical properties and reactivity of azines, **5**, 69
1,2,4-Thiadiazoles, **5**, 119
1,2,5-Thiadiazoles, chemistry of, **9**, 107
1,3,4-Thiadiazoles, recent advances in the chemistry of, **9**, 165
Thiathiophenes (1,6,6a*S*^{IV}-Trithiapentalenes), **13**, 161
1,2,3,4-Thiatriazoles, **3**, 263; **20**, 145
1,4-Thiazines and their dihydro derivatives, **24**, 293
4-Thiazolidinones, **25**, 83
Thienopyridines, **21**, 65
Thienothiophenes and related systems, chemistry of, **19**, 123
Thiochromanones and related compounds, **18**, 59
Thiocoumarins, **26**, 115

- Thiophenes, chemistry of, recent advances in, **1**, 1
- Thiopyrones (monocyclic sulfur-containing pyrones), **8**, 219
- Thioureas in synthesis of heterocycles, **18**, 99
- Three-membered rings with two heteroatoms, **2**, 83; **24**, 63
- Transition organometallic compounds in heterocyclic synthesis, use of, **30**, 321
- 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-Triazanaphthalenes, **10**, 149
- 1,2,3-Triazines, **19**, 215
- 1,2,3-Triazoles, **16**, 33
- 1,6,6a^{IV}-Trithiapentalenes, **13**, 161